CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

207962Orig1s000

SUMMARY REVIEW
Clinical Review, Cross-Discipline Team Leader, and Summary Division Director Review

<table>
<thead>
<tr>
<th>Date</th>
<th>February 28, 2018</th>
</tr>
</thead>
</table>
| From               | Sepideh Haghpanah, MD  
Janet Maynard, MD, MHS  
Ellen Fields, MD, MPH |
| Subject            | Cross-Discipline Team Leader Review |
| NDA/BLA # | 207962 (complete response submission) |
| Applicant          | Scilex Pharmaceuticals |
| Date of Submission | August 28, 2017 |
| PDUFA Goal Date    | February 28, 2018 |
| Proprietary Name / Established (USAN) names | ZTLido (lidocaine topical system) 1.8% |
| Dosage forms / Strength | One to three patches for up to 12 hours in a 24-hour period |
| Proposed Indication(s) | Relief of pain associated with post-herpetic neuralgia |
| Recommended:       | Approval |

**Materials Reviewed**

| Medical Officer Review | N/A |
| Statistical Review    | N/A |
| CMC Review            | Erika Englund (Drug Substance and Drug Product), James Norman (Process), Cassandra Abellard (Facility), Kalpana Paudel (Biopharmaceutics), Steve Kinsley ( Regulatory Business Process Manager), Ciby Abraham (Application Technical Lead), Caryn McNab (ORA Lead) |
| Microbiology Review   | N/A |
| Pharmacology Toxicology Review | Armaghan Emami, PhD, Jay Chang, PhD, Dan Mellon, PhD |
| Clinical Pharmacology Review | Wei Qui, PhD, Yun Xu, PhD |
| Office of Study Integrity and Surveillance Review | Himanshu Gupta, PhD, John Kadavil, PhD |
| Office of Prescription Drug and Promotion (OPDP) | L. Shenee Toombs, Sam Skariah |
| Division of Medical Policy Programs (DMPP) | LaShawn Griffiths, Barbara Fuller, Morgan Walker |
| OSE/DMEPA             | Millie Shah, PharmD, BCPS, Otto L. Townsend, PharmD |

Reference ID: 4227523
1. Introduction

ZTlido (lidocaine topical system) 1.8% is a new lidocaine patch developed for the relief of pain associated with post-herpetic neuralgia (PHN). Scilex Pharmaceuticals (Scilex) originally submitted a 505(b)(2) application for ZTlido on July 10, 2015, and received a complete response on May 10, 2016, for multiple deficiencies across disciplines, including clinical, clinical pharmacology, nonclinical, and product quality deficiencies. The current complete response submission was received on August 28, 2017.

In support of the 505(b)(2) application, Scilex has identified Lidoderm Patch 5% (NDA 20612; Teikoku Pharma) as the listed drug. Lidoderm Patch 5% was approved on March 19, 1999, for the relief of pain associated with PHN. ZTlido was designed to achieve comparable lidocaine systemic exposure to Lidoderm, but with less drug per patch (i.e., 36 mg/patch versus 700 mg/patch). The patch design is also intended to provide improved adhesion compared to Lidoderm. Three patches may be applied at a time, for up to 12 hours within a 24-hour period, which is consistent with the maximum recommended daily dose of Lidoderm.

The Applicant relies on the Agency's previous findings for efficacy and safety for Lidoderm and has not conducted efficacy or safety studies, beyond the dermal safety studies required for a new patch. The Applicant has also relied on the scientific literature and provided pharmacokinetic data to bridge ZTlido to Lidoderm. In addition to Lidoderm, products currently approved for the treatment of PHN are oral formulations of gabapentin (Neurontin, Horizant) and pregabalin (Lyrica), and capsaicin 8% patch (Qutenza).

The PDUFA goal date for this complete response is February 28, 2018, with a standard review clock.

2. Background

Regulatory History

Development of ZTlido occurred under IND 111537. There were numerous interactions between Scilex and the Division of Anesthesia, Analgesia, and Addiction Products (DAAAP) related to the development program of ZTlido. These are outlined in Dr. Muniz’s Clinical Review dated April 26, 2016, and Dr. Feeney’s Cross-Discipline Team Leader review dated April 28, 2016. Notable milestones include a pre-IND meeting in 2011, submission of the original IND in 2014, and a pre-NDA meeting in 2015.
In terms of the recent regulatory history, Scilex submitted the 505(b)(2) application for ZTlido on July 10, 2015, and received a complete response on May 10, 2016. Numerous deficiencies were identified across multiple disciplines. These deficiencies are described in the relevant sections below.

Following the complete response action, Scilex had a Type A meeting with the Division on August 24, 2016. Highlights of the discussion included:

- The Division clarified when Scilex must cite a listed drug and provide adequate patent certification.
- The Division agreed with the design of studies SCI-LIDO-ADH-001 (assessment of adhesion) and SCI-LIDO-HEX-001 (the effect of heat and exercise on pharmacokinetics).
- Agreement was reached on the design of the new relative bioavailability study (SCI-LIDO-PK-001), especially regarding exclusion of tape reinforcement.
- There was discussion of the dermal safety profile of ZTlido. The Division stated that whether or not an additional dermal safety study was done, the results from the previous dermal studies will be reflected in labeling.
- There was clarification of the non-clinical and CMC deficiencies and data necessary to address these deficiencies.

3. CMC/Device

The CMC review was conducted by several reviewers listed on the first page of this memo. Ciby Abraham, PhD was the Application Technical Lead. In the review of the original application, numerous deficiencies were noted by the CMC review team that precluded approval of this product from the CMC perspective. In the current complete response submission, these deficiencies have been addressed and the recommendation by the CMC review team is approval of this product from their perspective.

As per the CMC review:

The drug substance, Lidocaine is manufactured by [redacted] and is referenced in DMF# [redacted] (adequate, last reviewed 1/27/2017). Lidocaine is a white or almost white crystalline powder that is insoluble in water. Lidocaine is packaged in [redacted] . Lidocaine has a [redacted]-month retest period when stored at [redacted] °C.

The drug product, ZTlido (lidocaine topical system) is manufactured by Oishi Koseido Co., Ltd. ZTlido contains 36 mg of lidocaine drug substance compounded in an anhydrous adhesive system intended for topical route of administration. The drug product comprises of an adhesive material containing lidocaine that is applied to a
nonwoven cloth and covered with a polyethylene terephthalate release liner. The drug product contains 1.8% lidocaine in a 10 x 14 cm topical system, which can be cut into smaller sizes prior to removal of the release liner. Up to 3 topical systems may be applied for up to 12 hours in a 24 hour period. The applicant performed residual drug analysis on used patches (includes residuals from the skin and liners/envelopes) and a total of 18.44 mg of lidocaine was obtained for the 36 mg topical system.

<table>
<thead>
<tr>
<th>Component</th>
<th>Residual Drug (mg/patch)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Lidocaine Patch 1.8%</td>
</tr>
<tr>
<td>Used patches</td>
<td>17.70±2.96</td>
</tr>
<tr>
<td>Skin</td>
<td>0.53±0.21</td>
</tr>
<tr>
<td>Liners/envelopes</td>
<td>0.22±0.02</td>
</tr>
<tr>
<td>Total</td>
<td>18.44±2.94</td>
</tr>
</tbody>
</table>

The extractables/leachables were reviewed and found adequate by Dr. Erika Englund. Below is a summary of her extractables/leachables review: “The extractables study was conducted with the release liner, cloth backing, adhesive and envelope striped with an excess of inks used in the commercial packaging (study 0353). The components were extracted in an oven at 40°C for 48 hours in two separate solvent systems: (1) 0.9% w/v saline solution and (2) 70:30 isopropyl alcohol and 0.9% saline. The extracts were then tested by GC-MS, LC-MS (positive and negative ion mode and UV detection) and ICP-OES (inductively coupled plasma optical emission spectrometry). The only elemental impurity above the PDE in the extractables study was , and this was due to a suspected contamination (refer to document 053-01). The measured level of extracted from the iso-propanol and saline solution was mcg/system. This level of was not considered a potential safety issue by the non-clinical reviewer Armaghan Emami, Ph.D. No other elemental impurities were near the PDE. Since there were no elements detected in ICP-OES that were identified as a safety concern, the applicant’s proposal to not use this analytical method in the leachables study is acceptable from a CMC perspective. The agency had agreed that various batches at different time points could be used to support the 24 month shelf life, and based on the totality of evidence new batches of drug product might not be necessary to be placed on stability for the current NDA review. Three different drug product batches were tested at 3 month, 18 month, and 38 month testing points. Three expired batches at the 55 month time point were tested. The individual components in the formulation were tested for residual monomers and dimers. The only two detected (above ppm) were . In 2.3.P.2 the sponsor described that residual monomers were not detected in leachables analysis of the drug product. The description of the leachables/extractables study is adequate.”

Dr. Le Zhang reviewed the in vivo adhesion study and found it to be adequate. Below is Dr. Le Zhang’s conclusion on the in vivo adhesion study: “The study was suitably conducted for adhesion assessment (i.e. consistently spaced observations throughout
wear period, no overlays, adhesive tapes, bandages or similar products were applied during the application period, etc.). The adhesion analysis included all topical systems from 54 subjects and no systems were removed early for unacceptable irritation or dropped out of the study before the end of the 12-hour application. The clinical study report for study SCI-LIDO-ADH-001 was provided in Section 5.3.5.4. A single lidocaine topical system (1.8%) applied over a predetermined fixed area on subject’s left side or right side of the back (lower/mid back) according to randomization schedule and worn for the 12-hour study period. Adhesion assessment was done immediately after application (0 hour) and at 3, 6, 9 and 12 (before removal) hours after application with a window period ±15 minutes. The adhesion scores for all subjects are either 0 or 1, with 96% of 0’s and 4% of 1’s, indicating at least 75% adhesion for all systems at all times with 95% lower confidence limit 94.6%.”

An expiry of 24 months at 25°C is granted for ZTlido.

The Office of Compliance at The Center for Devices and Radiological Health (CDRH) completed the evaluation of this application and recommended that it was approvable from the perspective of Medical Device Regulations. Pre-approval inspections were conducted at two facilities (Combination Product Contract Manufacturer Oishi Koseido Co., Ltd 2539-1 Yamaura-Machi, Tosu, Saga, Japan and Quality Control Testing Laboratory 1 Chrome 933 Hon-Machi, Tosu, Saga, Japan) and both were classified as NAI with no 483 observations. It was noted that process validation (PV) was not completed at the time of the inspection, although a draft PV protocol was available for review. CDRH noted that there were no specific safety concerns related this.

The application was deemed adequate from a facilities standpoint. A review of the application and inspectional documents of the facilities responsible for manufacturing Lidocaine Patch per NDA 207962 has determined that there are no significant outstanding issues with the firms involved in the manufacturing of the product.

We concur with the conclusions reached by the chemistry review team regarding their recommendation for an approval action.

4. Nonclinical Pharmacology/Toxicology

The primary Pharmacology/Toxicology Review was performed by Armaghan Emami, PhD with secondary concurrence by Jay Chang, PhD and Dan Mellon, PhD. There were numerous pharmacology/toxicology issues in the original application that have been resolved in this complete response. The pharmacology/toxicology team recommends an approval action.

As per Dr. Emami’s review:

- The complete response letter dated May 10, 2016, included five nonclinical deficiencies, which are briefly summarized below:

Reference ID: 4227523
1. Inadequate safety justification was provided for the proposed drug product degradant specification of 2,6-xylidine, a known rat carcinogen.

2. Inadequate safety justification was provided for the drug product degradants, Impurities \[^{(b)}\] and \[^{(b)(4)}\] which exceeded the qualification threshold per the ICH Q3B(R2) guidance.

3. Inadequate data were provided to support the systemic safety of the dipropylene glycol, isostearic acid, SIS block copolymer, and terpene resin excipients based on the intended clinical use of the product.

4. Inadequate information was provided regarding polyisobutylene in the drug product formulation in to permit a complete safety evaluation of this excipient.

5. Inadequate leachables NDA data were submitted with the original NDA to permit adequate review.

In addition, the complete response letter reminded the Applicant that given the change in duration of the indication during the development of this product, chronic toxicology (6-month rat and 9-month minipig) and carcinogenicity studies in two species (at least one dermal) would be required for any new excipients. Although the Applicant was encouraged to initiate those studies as soon as possible, if they were not completed by the time of the resubmission, the Division noted that they may be completed as PMRs.

With this resubmission, the Applicant addressed each deficiency with sufficient information for review.

The outstanding deficiencies (Items 1 and 2 above) regarding the drug product specifications have been adequately addressed via new genetic and general toxicology studies and the Applicant’s risk assessment for 2,6-xylidine. Therefore, the drug substance and drug product specifications are acceptable from a pharmacology toxicology perspective.

Outstanding Deficiencies 3 and 4 above focused on the safety assessment of the “new” (i.e., novel use) excipients. To address these deficiencies, the Applicant submitted a literature-based toxicological risk assessment to address the systemic safety of dipropylene glycol, isostearic acid, SIS block copolymer, terpene resin, and polyisobutylene. Adequate data have been provided to justify the safety of the drug product formulation excipients. This safety assessment was bolstered by an adequate leachable assessment. In brief, adequate data were provided to characterize the levels of compounds that can be leached from the patch and presumably absorbed by the patients. Review of the risk assessment and the leachable data addressed most of the concerns. However, the data do suggest significant levels of \[^{(b)(4)}\] can be released from the patch. Existing toxicity data in the published literature address the general toxicity and carcinogenicity of the compound. In terms of reproductive and developmental toxicity, definitive embryo-fetal development studies were completed by the National Toxicology Program. In addition, a multigenerational study in rats has been reviewed by the Organization for Economic Co-operative Development (OECD).
that includes many of the standard endpoints in modern fertility and early embryonic development studies and includes some post-natal development endpoints as well. Given the use of \( \text{(b)(4)} \) in other transdermal drug products at comparable levels and based on a weight-of-evidence approach, no further studies are necessary to qualify this excipient for this drug product.

As noted in previous reviews, the Division concluded that post-herpetic neuralgia was no longer viewed as a subchronic indication based on clinical use data. Because this change occurred near the time the Applicant was intended to originally submit their NDA, the Division agreed to allow chronic toxicology and carcinogenicity studies for new excipients to be completed post-marketing. To address the systemic safety of the new excipients, the Applicant submitted a toxicological risk assessment based on literature, proposed to conduct the requested 9-month minipig study with the to-be-marketed drug product, and requested a waiver of the 6-month rodent toxicology study and the systemic rodent carcinogenicity studies. Upon review, the review team concluded that adequate data exist to support a waiver of the 6-month and systemic carcinogenicity studies; however, the 9-month minipig study cannot be waived. These may still be completed as PMRs, as previously agreed. Deficiencies 3 and 4 above have been adequately addressed. The remaining concerns with excipients may be addressed via PMRs.

As noted in the complete response letter, adequate leachable studies were required to support the safety of ZTlido. The studies were reviewed this cycle and determined to be adequately completed from a CMC perspective. The submitted toxicological risk assessment for the compounds that detected above the requested qualification threshold of 5 mcg/day was deemed adequate with one exception. The compound contains a structural alert for mutagenicity. The compound was detected in the pilot leachable study, but the limit of detection in the pivotal leachable study could not confirm that levels would be below the ICH M7 threshold of toxicological concern of NMT 10 mcg/day for a drug product with expected duration of use between 1 and 10 years. Based on the data, it is possible that a person would be exposed to up to mcg/day of this compound. The Applicant supplied data on a surrogate molecule suggesting that the surrogate, which also contained an moiety has been reported to be negative in an Ames assay.

These data are supportive. However, definitive data via an in vitro bacterial reverse mutation assay (Ames test) should be submitted to refute the QSAR prediction of potential mutagenic concern. Because this is a theoretical concern based on limits of detection in the assay, the worst-case level being at most mcg/day, and given the data on the surrogate, the definitive study may be complete as a PMR. Otherwise, the Applicant adequately addressed Deficiency 5 listed above.
To comply with the Pregnancy and Lactation Labeling Rule (PLLR) the Applicant submitted a literature review for lidocaine and incorporated information into the draft labeling. This information has been reviewed by the nonclinical team.

The non-clinical team has recommended the following PMRs:

1. Conduct a 9-month minipig study using the to-be-marketed drug product. The study should mimic the clinical use of the drug product with repeated applications to the same location as per the product labeling.

2. Conduct a 2-year dermal carcinogenicity study to evaluate the carcinogenic potential of terpene resin, dipropylene glycol, SIS block copolymer, isostearic acid, and polyisobutylene.

3. Conduct an Ames assay for or provide adequate data based on validated analytical methods that the levels of this compound that can leach from the patches at the maximum daily dose (3 patches per day) remain below 10 mcg/day.

From the nonclinical pharmacology toxicology perspective, the NDA is recommended for approval with the PMRs listed above. We concur with the conclusions reached by the nonclinical pharmacology toxicology team.

5. Clinical Pharmacology/Biopharmaceutics

The clinical pharmacology review was conducted by Wei Qiu, PhD, with secondary concurrence from the clinical pharmacology team leader, Yun Xu, PhD. They have found the complete response submission to be acceptable from a clinical pharmacology perspective.

Scilex developed ZTLido (1.8% lidocaine patch) to be bioequivalent to Lidoderm (5% lidocaine patch) to rely in part on the efficacy and safety of the Lidoderm patch. The Agency agreed that if the Applicant could demonstrate a scientific bridge establishing equivalent exposure between the two products, no additional efficacy studies would be required. The Applicant was advised during the PIND meeting that in the comparative bioavailability (BA) study intended to support bioequivalence, the Lidoderm patch must be applied as directed in the label without tape or other reinforcements. At the PNDA meeting, the Applicant informed the Agency that the Lidoderm patch was reinforced with tape in the comparative BA study (SCI-LIDO-PK-001). At that time the Applicant was advised that they would need to provide evidence to justify that the use of tape would not affect lidocaine absorption from the Lidoderm patch. The Applicant did not provide adequate justification for the use of tape in the comparative BA study.

In the complete response letter dated May 10, 2016, Deficiency #4 stated as “the comparative bioavailability study, SCI-LIDO-PK-001, intended to bridge to the Agency’s previous findings of efficacy and safety for Lidoderm patch 5%, cannot be used to establish bioequivalence because surgical tape was used to secure the Lidoderm 5% patches, and adequate evidence was
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NDA 207962 ZTlido Patch Complete Response Resubmission

not provided to justify that the use of tape would not affect lidocaine absorption from Lidoderm patch 5%. To address this deficiency, conduct a new adequately-designed comparative bioavailability study to demonstrate equivalent systemic exposure to Lidoderm patch 5%. The list drug product, Lidoderm patch 5%, must be used according to the approved package insert (e.g., without use of an overlay or tape). Additional data from Study SCI-LIDO-HEX-001 submitted during the review cycle were not reviewed. You may reference the submission as part of your response to the deficiencies cited in this letter.”

In this resubmission, the Applicant submitted a comparative bioavailability study (SCI-LIDO-PK-002A) to address the Deficiency #4 regarding an appropriate PK bridge to the list drug product, Lidoderm patch 5%.

Study SCI-LIDO-PK-002A demonstrated that three patches of lidocaine patch 1.8% provided comparable lidocaine systemic exposure as three patches of Lidoderm patch 5% with no tape reinforcement. Study SCI-LIDO-PK-002A was a single-dose, two-way cross-over design with the application of three patches of either lidocaine patch 1.8% or the listed drug product, Lidoderm patch 5%. There was a washout period of 7 days between treatments. Each patch was applied to a defined area of normal skin on the back of each volunteer for 12 hours. See the clinical pharmacology review for additional details regarding the study design.

The mean lidocaine plasma concentration-time profiles are shown in Figure 1. Three patches of lidocaine patch 1.8% (test) exhibited equivalent lidocaine Cmax and AUC values and similar Tmax values to those for three patches of Lidoderm patch 5% (reference) without tape reinforcement (Table 1 and Table 2). The Cmax, AUCt, and AUCl for lidocaine patch 1.8% and Lidoderm patch 5% met bioequivalent (BE) criteria. The 90% confidence intervals for the geometric mean ratio for Cmax, AUCt, and AUCl all fell within the 80 to 125% BE limit.
Figure 1: Mean Lidocaine Plasma Concentration (ng/mL) Time Profiles for Three Lidocaine Patches 1.8% (test) and Three Patches of Lidoderm Patch 5% (reference) Applied for 12 Hours (Study SCI-LIDO-PK-002A)

Table 1: Mean (SD) Lidocaine PK Parameters for Three Patches of Lidocaine

<table>
<thead>
<tr>
<th>Pharmacokinetic Parameters</th>
<th>Lidocaine Patch 1.8% Mean ± SD (N=54)</th>
<th>Lidoderm Patch 5% Mean ± SD (N=54)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C_max (ng/mL)</td>
<td>75.1 ± 28.0</td>
<td>86.6 ± 42.3</td>
</tr>
<tr>
<td>T_max (hr)</td>
<td>13.9 (4.0, 18.0)</td>
<td>11.0 (4.0, 17.9)</td>
</tr>
<tr>
<td>AUC_(0-t) (ng/hr/mL)</td>
<td>1242.9 ± 432.5</td>
<td>1420.8 ± 586.0</td>
</tr>
<tr>
<td>AUC_(0-&gt;) (ng/hr/mL)</td>
<td>1253.7 ± 432.5</td>
<td>1435.5 ± 588.9*</td>
</tr>
<tr>
<td>T_(1/2) (hr)</td>
<td>5.4 ± 1.0</td>
<td>6.2 ± 1.6*</td>
</tr>
</tbody>
</table>

* N = 53

T_max is reported as median value (range)

Source: Clinical Pharmacology Review dated January 30, 2018, Table 1, page 3

Table 2: Summary of Equivalence Analyses for the Lidocaine PK of Three Patches of Lidocaine Patch 1.8% and Three Patches of Lidoderm Patch 5% (Study SCI-LIDO-PK-002A)

<table>
<thead>
<tr>
<th>Pharmacokinetic Parameter</th>
<th>Ratio of Geometric Means</th>
<th>90% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Lower</td>
<td>Upper</td>
</tr>
<tr>
<td>C_max (ng/mL)</td>
<td>0.90</td>
<td>0.85</td>
</tr>
<tr>
<td>AUC_Co (ng/hr/mL)</td>
<td>0.89</td>
<td>0.84</td>
</tr>
<tr>
<td>AUC_(0-&gt;) (ng/hr/mL)</td>
<td>0.88</td>
<td>0.84</td>
</tr>
</tbody>
</table>

Source: Clinical Pharmacology Review dated January 30, 2018, Table 2, page 4

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Therefore, the Applicant has adequately established a PK bridge to the Agency’s previous findings on efficacy and safety for Lidoderm patch 5%.

Study SCI-LIDO-HEX-001 evaluated the effect of heat and exercise on lidocaine exposure. The study was a three-way cross-over design with three patches of lidocaine patch 1.8% applied to a defined area of normal skin on the back of each volunteer for a treatment duration of 12 hours under three conditions (moderate exercise [Treatment A], moderate heat [Treatment B], and normal conditions [Treatment C]). During Treatment A, subjects exercised on a bike for 30 minutes (target heart rate: 108 bpm) immediately after patch application and at 2.50, 5.50, and 8.50 hours post-patch application. During Treatment B, a standard 3-setting heating pad, used in accordance with the manufacturer’s instructions at a medium setting, was placed on top of the patch immediately after patch application and at 8.50 hours post-application. The heating pad was left in place for 20 minutes. A blanket/towel was placed between the patches and heating pad to reduce the chance of skin burning. No stress conditions were applied during Treatment C (normal conditions). There was a washout period of 7 days between treatments. No tape reinforcement was used during the study. See the clinical pharmacology review for additional details regarding the study design.

The mean lidocaine plasma concentration-time profiles evaluating the effects of heat and exercise on lidocaine exposure are shown in Figure 2. PK results and statistical analysis results for equivalence assessment of lidocaine PK parameters including AUClast, AUCinf, and Cmax are presented in Table 3 and Table 4. Use of heating pad on the patches increased lidocaine Cmax by 46% but did not affect the AUCt or AUCinf as compared to normal conditions. Moderate exercise did not affect lidocaine PK. The product labeling will reflect the impact of exercise and heat on lidocaine exposure.

**Figure 2: Mean Lidocaine Plasma Concentration (ng/mL) Time Profiles for Three Patches of Lidocaine Patch 1.8% Applied for 12 Hours Under Exercise (A), Heat (B), or Normal Conditions (C) (Study SCI-LIDO-HEX-001)**

Source: Clinical Pharmacology Review dated January 30, 2018, Figure 2, page 9
Table 3: Summary of Lidocaine PK Parameters for the Effect of Heat (Treatment B) and Exercise (Treatment A) on Lidocaine PK of Three Patches of Lidocaine Patch 1.8% in Comparison to Normal Condition (Treatment C) (Study SCI-LIDO-HEX-001)

<table>
<thead>
<tr>
<th>Parameter (Unit)</th>
<th>Treatment (A)</th>
<th>Treatment (B)</th>
<th>Treatment (C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cmax (ng/mL)</td>
<td>90.477 ± 25.413083</td>
<td>160.275 ± 100.061002</td>
<td>97.593 ± 36.869199</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;0→Inf&lt;/sub&gt; (hr ng/mL)</td>
<td>1328.80587 ± 461.660141</td>
<td>1718.70939 ± 1004.00502</td>
<td>1487.39290 ± 590.006714</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;0→Inf&lt;/sub&gt; (hr ng/mL)</td>
<td>1344.07581 ± 458.186710</td>
<td>1731.27168 ± 1005.03640</td>
<td>1501.09829 ± 588.427583</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;0→Inf&lt;/sub&gt; (hr ng/mL)</td>
<td>1.36226 ± 2.211383</td>
<td>0.89693 ± 1.112316</td>
<td>1.07191 ± 1.534819</td>
</tr>
<tr>
<td>Tmax (hr)</td>
<td>9.00 (9.00-18.00)</td>
<td>9.00 (9.00-16.05)</td>
<td>11.50 (9.00-14.00)</td>
</tr>
<tr>
<td>Keal (hr&lt;sup&gt;-1&lt;/sup&gt;)</td>
<td>0.12803 ± 0.0024237</td>
<td>0.13509 ± 0.029065</td>
<td>0.13874 ± 0.029814</td>
</tr>
<tr>
<td>t&lt;sub&gt;1/2&lt;/sub&gt; (hr)</td>
<td>5.60 ± 1.1134</td>
<td>5.39 ± 1.3381</td>
<td>5.23 ± 1.2029</td>
</tr>
</tbody>
</table>

Source: Clinical Pharmacology Review dated January 30, 2018, Table 3, page 4

Table 4: Summary of Equivalence Analyses for the Effect of Heat (Treatment B) and Exercise (Treatment A) on Lidocaine PK of Three Patches of Lidocaine Patch 1.8% in Comparison to Normal Condition (Treatment C) (Study SCI-LIDO-HEX-001)

<table>
<thead>
<tr>
<th>PK Parameter</th>
<th>Ratio % (A/C)</th>
<th>90% CI (A/C)</th>
<th>Ratio % (B/C)</th>
<th>90% CI (B/C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cmax</td>
<td>95.14</td>
<td>80.30 – 112.73</td>
<td>146.57</td>
<td>123.71 – 173.66</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;0→Inf&lt;/sub&gt;</td>
<td>90.25</td>
<td>79.65 – 102.26</td>
<td>108.02</td>
<td>95.34 – 122.40</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;0→Inf&lt;/sub&gt;</td>
<td>90.53</td>
<td>80.15 – 102.25</td>
<td>107.83</td>
<td>95.46 – 121.79</td>
</tr>
</tbody>
</table>

Source: Clinical Pharmacology Review dated January 30, 2018, Table 4, page 5

The Office of Clinical Pharmacology/Division of Clinical Pharmacology 2 finds the resubmission acceptable. We concur with the conclusions reached by the clinical pharmacology reviewers.

6. Clinical Microbiology

No new clinical microbiology data were included in the application.

7. Clinical/Statistical- Efficacy

There were no efficacy studies submitted in this application as the Applicant relied on the Agency’s previous findings of efficacy for the listed drug, Lidoderm 5% patch. In a single-dose, crossover study, ZTlido 1.8% demonstrated equivalent exposure (AUC) and peak concentration (Cmax) of lidocaine to Lidoderm (lidocaine patch 5%). Thus, the Applicant has established an adequate PK bridge with the Lidoderm 5% patch and it is reasonable to rely on the Agency’s previous findings of efficacy of the Lidoderm patch 5% for the treatment of pain of PHN. The proposed indication and dosing regimen for ZTlido are identical to those for Lidoderm.
8. Safety

The Applicant relied on the systemic safety for the listed drug Lidoderm 5% patch given the equivalent exposure to lidocaine between ZTlido and Lidoderm. In the original submission, the only safety data collected were limited to the comparative BA study in healthy volunteers (SCI-LIDO-PK-001), and three dermal safety studies in healthy volunteers that assessed local safety and tolerability (SCI-LIDO-DERM-001 [dermal sensitization], SCI-LIDO-PHOTO-001 [photoallergy], and SCI-LIDO-PHOTO-002 [phototoxicity]). In the current submission, the safety data are from two BA studies in healthy volunteers (SCI-LIDO-PK-002A and SCI-LIDO-PK-002B), an adhesion study (SCI-LIDO-ADH-001), and a pharmacokinetic study evaluating the effect of exercise and heat (SCI-LIDO-HEX-001).

This review will outline the studies previously conducted and reviewed, followed by a review of the studies submitted in the complete response, and then a summary of the overall safety.

SUMMARY OF PREVIOUS STUDIES
Studies SCI-LIDO-PK-001, SCI-LIDO-DERM-001, SCI-LIDO-PHOTO-001, and SCI-LIDO-PHOTO-002 were reviewed during the initial submission and are summarized in Table 5.
Table 5: Summary of Previous Studies

<table>
<thead>
<tr>
<th>Study ID / Site</th>
<th>Overview / Design Treatment / Control</th>
<th>1º Objective</th>
<th>Duration / Exposure</th>
<th>Population Total</th>
<th>Note / Summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>SCI-LIDO-PK-001</td>
<td>OL, cross-over, BE Cohort 1, Part 1: Lidocaine IV 0.7 mg/kg single bolus dose Cohort 1, Parts 2 and 3 and Cohort 2: ZTlido vs. Lidoderm</td>
<td>Cohort 1: PK Cohort 2: PK with heat, exercise, and normal condition</td>
<td>12 w / 12 h Cohort 1: 58 Cohort 2: 14 18-65 y/o</td>
<td>72</td>
<td>Main issues: 1- Use of tape 2- Patch was applied after heat &amp; exercise AE’s and Safety: Cohort 1: 17 AEs in 12 subjects- mild Cohort 2: 7 AEs in 5 subjects - mild</td>
</tr>
<tr>
<td>SCI-LIDO-DERM-001</td>
<td>R, evaluator-blinded, controlled, within-subject comparison 3 patches for 48 hours ZTlido vs Lidoderm</td>
<td>Cohort 1: Adhesion &amp; Irritation/Sensitization Cohort 2: Irritation/Sensitization</td>
<td>6 w / 48 h x 21 d Cohort 1: 41 Cohort 2: 207 ≥ 18 years</td>
<td>248</td>
<td>Main issues and DDDP’s comment: 1- Lidocaine 1.8% patch was not sensitizing 2- Potential for severe irritation should be added to labeling. AE’s and Safety: 24 AEs in 20 subjects: - 3 severe (skin erosion/ reaction) - 12 moderate AEs - 9 mild AEs 4 discontinuations due to AEs No deaths or SAEs ZTlido was more irritating than the lidocaine patch 5%</td>
</tr>
<tr>
<td>SCI-LIDO-PHOTO-001</td>
<td>R, evaluator-blinded, controlled, within-subject comparison ZTlido vs Lidoderm</td>
<td>Photosensitization/ Photoallergic reaction</td>
<td>6 w / 12 h</td>
<td>60</td>
<td>DDDP’s comment: ZTlido was not a photoallergen.</td>
</tr>
<tr>
<td>SCI-LIDO-PHOTO-002</td>
<td>R, evaluator-blinded, controlled, within-subject comparison ZTlido vs Lidoderm</td>
<td>Phototoxicity</td>
<td>4 d / 12 h</td>
<td>32</td>
<td>DDDP’s comment: ZTlido was not phototoxic.</td>
</tr>
</tbody>
</table>

Abbreviations: OL=open label; BE=bioequivalence; PK=pharmacokinetic; w=week; h=hour; AEs=adverse events; SAEs=serious adverse events; d=days; DDDP=Division of Dermatology and Dental Products; NJ=New Jersey; FL=Florida

Source: Reviewer generated

The key issues and observations from these studies will be reviewed here. Refer to clinical review dated 04/26/2016 by Dr. Javier Muniz for additional details.

**Study SCI-LIDO-PK-001**
Phase 1, Randomized, Comparative Pharmacokinetic (PK) Study of Bolus Intravenous Lidocaine 0.7 mg/kg, Lidocaine Patch 1.8%, and Lidocaine Patch 5% (Lidoderm) in Healthy Subjects and an Evaluation on the Effects of Heat and Exercise on the Pharmacokinetics of Lidocaine Patch 1.8% in Healthy Subjects
Cohort 1 (PK): (N=58)
- Part 1: Subjects received a single bolus of lidocaine IV 0.7 mg/kg
- Part 2: A set of 3 patches of either lidocaine patch 1.8% or Lidoderm 5% were applied for 12 hours. If needed tape or overly was used.
- Part 3: Subjects crossed-over to the patch not placed in Part 2

Cohort 2 (Heat and Exercise effect): (N=14)
- Heat treatment with a heating pad was applied to each subject’s back for 15 minutes. Immediately after the heat treatment, 3 lidocaine patches (1.8%) were applied for 12 hours.
- The subjects completed an exercise regimen (walking on treadmill at a moderate pace for 20 minutes). Then 3 lidocaine patches 1.8% were applied to the subjects’ back.

Assessments:
- PK data up to 48 hours
- Safety and tolerability

Safety Results:
There were no deaths or serious adverse events (SAEs). In Cohort 1, 12 subjects (20.7%) experienced a total of 17 AEs. More subjects (6, 10.5%) experienced an AE in the Lidoderm 5% group than the lidocaine 1.8% group (2 subjects, 3.6%). One subject experienced urticaria with IV lidocaine (considered unrelated to study drug) and discontinued the study. In addition, there was one subject who developed urticaria in the lidocaine 1.8% group. In Cohort 2, 5 subjects (35.7%) experienced a total of 7 AEs. All the AEs in Cohort 1 and Cohort 2 were mild in intensity.

Summary and Conclusion:
Conclusions from this study are limited given that tape or overlay were used to secure the patches and due to the limited size of the study. To address this issue, the Division requested that the Applicant provide adequate PK bridging data without use of tape and assess the effect of heat and exercise on the pharmacokinetics of lidocaine while wearing the patches.

II- SCI-LIDO-DERM-001 (DS103214)
Phase I, Multi-center, Repeat Insult Patch Test (RIPT) and Adhesion of Lidocaine Patch 1.8% and its Comparator Lidocaine Patch 5% (Lidoderm) in Healthy Subjects

Objectives:
Primary: To determine the irritation and sensitization potential of lidocaine patch 1.8% vs. Lidoderm

Secondary: To evaluate the adhesion of lidocaine patch 1.8% vs. Lidoderm

Cohort 1 (adhesion and irritation/sensitization): (N=41)
- Adhesion: Lidocaine patch 1.8% and Lidoderm were applied for 48-hour period to evaluate adhesion performance.
- Sensitization: Each subject received $\frac{1}{4}$ (9 mg) patch of lidocaine 1.8%, and $\frac{1}{4}$ patch (175 mg) of Lidoderm every 48 - 72 hours over a 21-day induction phase (a total of 9 patch applications).

**Cohort 2 (irritation/sensitization):** (N=207)
- Subjects received $\frac{1}{4}$ patch lidocaine patch 1.8%, and $\frac{1}{4}$ patch (175 mg) Lidoderm every 48-72 hours over a 21-day induction phase (a total of 9 patch applications).

**Assessment:**
- Irritation/ Sensitization
- Adhesion
- Safety (AEs) and tolerability

**Safety Results:**
The irritation/sensitization data included 248 subjects. There were no deaths or serious adverse events (SAEs). Twenty-four (24) AEs were reported in 20 subjects (11 treatment-related AEs in 10 subjects) including: 3 severe AEs in 3 subjects (skin erosion, skin blister, and skin erythema), 12 moderate AEs, and 9 mild AEs. Four AEs led to discontinuation of study medication in 4 subjects; one of them had a severe AE (application site reaction). In the review of the original application, three dermatologic events stood out as significant and related to ZTlido. These AEs included skin erosion (subject  and ) and two application site reactions (subjects  and ). These adverse reactions were described in detail by the clinical team, including Dr. Fields in the Division Director review. Given the cases of severe skin irritation, the Complete Response letter instructed the Applicant to provide a risk-benefit analysis addressing the potential benefits of ZTlido that would offset concerns about the dermal safety profile. For the three significant dermatologic events with ZTlido during study SCI-LIDO-DERM-001, the Applicant was asked to include a better characterization of the three events, detailing the history of the dermal lesions, any interventions used to treat the lesions, and the eventual outcome for each of the three subjects. A summary of these cases is included below:

**Subject  and :** This was a 67-year-old black female who experienced erosion at the ZTlido application site (Site 2; abrasions) during SCI-LIDO-DERM-001. The AE began on Day 5 of the study and ended on Day 8. The subject had abrasions as a result of scratching, provoked by localized pruritus. There were no signs of infections at the site and no additional treatment to the site was recommended. The intensity of the AE was severe and definitely related to the study product. The dose was not changed. The AE resolved and the subject recovered and she could continue in the study. There were no other severe AEs observed for this subject after the application site was moved.

**Subject  and :** This was a 52-year-old white female who experienced an adverse event of application site reaction (on the ZTlido patch site) during SCILIDO-DERM-001. The duration...
of the AE was from study Day 14 to 33. The AE was considered severe and probably related to
the test article by the investigator. Treatment was withdrawn and concomitant medication was
given to treat the event. The subject initially experienced pruritus associated with burning and
blisters on Day 14 and removed the patch on Day 15 at home. On Day 17, the subject
presented to the clinic. Examination of the former patch site revealed a localized reaction on
the left lateral lower back site with presence of erythematous, grouped vesicles at the base of
the site. The subject discontinued from the study and advised to use Domeboro soaks and a
topical antibiotic ointment on the site.

Subsequent examination of the site revealed continued erythema and presence of dried
vesicles. The subject was instructed to continue with the topical treatment. On Day 26, the
subject presented to the clinic reporting continued application of a topical antibiotic to the site
as well as a home remedy (vinegar) and reported less discomfort at the site. Examination of
the site revealed a further decrease in erythema and only isolated erythematous papules at
the sites of prior vesicles. The use of the topical antibiotic and home remedy was discontinued on
Day 30. The patch site reaction was noted to have resolved at the subject’s Day 33 visit.

Subject: This was a 67-year-old white female who experienced an adverse event of
application site reaction (on the ZTlido patch site) during SCILIDO-DERM-001. The duration
of the AE was from study Day 25 to 51. The AE was considered moderate and probably
related to the test article by the investigator. Treatment was withdrawn and medication was
given to treat the event. The subject discontinued from the study.

The subject presented to the clinic on Day 20 and reported developing moderate erythema and
one small bulla at the patch site after the rest period on Day 25. Upon examination, the left
lateral lower back patch site was noted to have erythema and small bullae. The subject was
instructed to treat the site with 1% hydrocortisone cream and a triple antibiotic ointment twice
daily. On Day 36, the subject returned for a follow-up visit and the small bullae was found to
have resolved and the erythema diminished but remained visible. The subject was instructed
to stop the triple antibiotic ointment and continue applying hydrocortisone 1% cream twice
daily.

On Day 44, examination of the site revealed trace erythema and adjacent to the patch site was
a non-inflamed flesh colored seborrhea keratosis. The examining physician suspected the
bullae noted on Day 29 were actually seborrheic keratosis. The subject was discharged with
no further instructions for treatment. In a telephone follow-up, the subject reported resolution
reaction as of Day 51 with no further changes to health or medication.

Summary and Conclusion:
Under the exaggerated conditions of the study (each patch applied for 48-72 hours over 21
days; a total of 9 applications), three subjects experienced significant dermatologic events
attributed to ZTlido. There was no sensitization to any of the patches. However, ZTlido was
associated with a higher proportion of subjects with an irritation score of 3 or above compared
to Lidoderm (8% versus 0%). ZTlido was significantly more irritating than Lidoderm, with
the mean cumulative irritation scores of 0.37 and 0.04 respectively (<0.0001).
The Division of Dermatology and Dental Products (DDDP) reviewed the dermal safety studies in the first review cycle and recommended that potential for severe irritation of Lidocaine 1.8% be included in product labeling. As noted in the Division Director review dated 05/10/2016, “severe reactions occurred under the exaggerated conditions of the dermal safety study (each patch applied for 48-72 hours …, whether actual use of the product as directed (patch applied for 12 hours out of each 24) will result in these severe reactions is unknown.”

- Adhesion
The adhesion assessment in this study were conducted incorrectly, as adhesion was assessed at 48 hours, rather than at 12 hours, which is the duration of patch application clinically. A new assessment of the adhesion profile of the product was included as a deficiency in the complete response.

III **SCI-LIDO-PHOTO-001 (PB710314)**
A 6-Week, Randomized Study to Evaluate the Potential of Lidocaine Patch 1.8% and its comparator Lidocaine Patch 5% (Lidoderm) to Induce a Photoallergic Skin Reaction in Healthy Volunteers, Using a Controlled Photopatch Test Design

N: 54

Assessment:
- Photosensitization response
- Local tolerability
- Adverse events

Safety Results: There were no deaths or SAEs. Two AEs were reported in 2 subjects during the 6-week study; one subject had hand pain and the other subject had a mild “photosensitivity reaction” which was localized at the Lidocaine 1.8% patch site. This reaction occurred after patch application and prior to irradiation during the Challenge Phase. DDDP felt that the etiology of this adverse event was not clear.

Summary and Conclusion:
DDDP concluded that the results show that Lidocaine 1.8% patch was not a photoallergen.

IV **Study SCI-LIDO-PHOTO-002 (PB610314)**
A 4-Day, Randomized Study to Evaluate the Irritation Potential of Lidocaine Patch 1.8% and its Comparator Lidocaine Patch 5% (Lidoderm) when Application to Skin is Followed by Light Exposure in Healthy Volunteers, Using a Phototoxicity Patch Test

N: 32

Assessment:
- Phototoxicity
- Local tolerability
- Adverse events

**Safety Results:** There was 1 mild AE (nausea) unrelated to the study treatment. The Applicant concluded that there was no indication of phototoxicity present among the subjects in this study.

**Summary and Conclusion:**
DDDP concluded that lidocaine patch 1.8% was not phototoxic.

**COMPLETE RESPONSE (CR) LETTER and RESUBMISSION**
The Division issued a Complete Response (CR) letter on 05/10/2016 that included multiple deficiencies across disciplines. The clinical deficiency was regarding adhesion data. The Applicant needed to provide adhesion data after 12 hours of patch use to be consistent with the proposed labeling.

**CURRENT STUDIES**
In response to the Agency’s CR letter, the Applicant completed four additional studies that are summarized in Table 6.
Table 6: Summary of Current Studies

<table>
<thead>
<tr>
<th>Study ID / Site</th>
<th>Overview / Design / Treatment / Control</th>
<th>1st Objective</th>
<th>Duration / Exposure</th>
<th>Population Total</th>
<th>Notes / Summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>SCI-LIDO-PK-002A</td>
<td>OL, cross-over, BE ZTlido, Lidoderm, and Versatis (lead-in portion only)</td>
<td>PK</td>
<td>2.5 w / 12 h</td>
<td>Total: 90</td>
<td>BA/BE study without tape - ZTlido and Lidoderm BE Safety: 2 AE (mild); 1 ZTlido / 1 Lidoderm</td>
</tr>
<tr>
<td>SCI-LIDO-PK-002B</td>
<td>OL, cross-over, BE ZTlido vs. Versatis</td>
<td>PK</td>
<td>7 w / 12 h</td>
<td>53</td>
<td>BA/BE study without tape Safety: 8 AE (mild); 5 ZTlido / 3 Versatis</td>
</tr>
<tr>
<td>SCI-LIDO-ADH-001</td>
<td>OL, single-application adhesion study ZTlido</td>
<td>Adhesion</td>
<td>1 d / 12 h</td>
<td>54</td>
<td>12 h adhesion study - &gt;90% adhesion; &gt;90% subjects Safety: No AE (Max age 58, Mean 30)</td>
</tr>
<tr>
<td>SCI-LIDO-HEX-001</td>
<td>OL, R, 3 Tx cross-over, PK &amp; adhesion study A: with exercise B: with heat C: normal condition ZTlido</td>
<td>PK and adhesion</td>
<td>2.5 w / 12 h</td>
<td>12</td>
<td>Heat and Exercise effect on PK - increased drug exposure with heat, but returns to normal levels once the heat source is removed. Safety: No effect on PK with exercise (Max age 62, Mean 46)</td>
</tr>
</tbody>
</table>

Abbreviations: OL=open label; BE=bioequivalence; R=randomized; Tx=treatment; PK=pharmacokinetic; w=week; h=hour; BA=bioavailability; AEs=adverse events; NJ=New Jersey; MN=Minnesota Source: Reviewer generated

I- Study SCI-LIDO-PK-002A
Phase 1, Randomized, Comparative Pharmacokinetic Study of Lidocaine Patch 1.8% (ZTlido) and Lidocaine Patch 5% (Lidoderm) in Healthy Subjects

Objectives:

- **Primary:**
  - To characterize and compare the single-dose pharmacokinetics of lidocaine patch 1.8% (investigational product / test) versus Lidoderm and determine the apparent dose based on patch residual drug analysis

- **Secondary:**
  - To evaluate bioequivalence between lidocaine patch 1.8% and Lidoderm
  - To evaluate and compare the safety following a single dose of lidocaine patch 1.8% and Lidoderm
To evaluate skin irritation of lidocaine patch 1.8% and Lidoderm

As a Lead-in, to establish skin swabbing procedures for residual drug once patches are removed for lidocaine patch 1.8% (investigational product/test), Lidoderm, and Versatis Medicated plaster 5% (Versatis is the EU trade name for Lidoderm)

**Treatment:** 3 lidocaine patches 1.8% or 3 Lidoderm 5% patches (or Versatis)

**Duration of study:** 2.5 weeks (12 hours for each part, 7-day washout)

**Duration of exposure to Lidocaine patch 1.8%:** 12 hour

**Key inclusion and exclusion criteria:** healthy males and non-pregnant, non-nursing females who were between the ages of ≥18 and ≤65 years of age for Lead-In part, and ≥18 years of age for the pharmacokinetic part.

**Design:** Study SCI-LIDO-PK-002A was a replicate of Study SCI-LIDO-PK-001 except for the following differences:
1. Study SCI-LIDO-PK-001 utilized tape reinforcement during the administration period while Study SCI-LIDO-PK-002A excluded tape reinforcement;
2. Study SCI-LIDO-PK-001 included an IV lead-in while Study SCI-LIDO-PK-002A did not;
3. Study SCI-LIDO-PK-002A included a comparative residual lidocaine analysis from used patches; skin after patch removal; patch liners; and patch envelopes while Study SCI-LIDO-PK-001 only included residual patch analysis;
4. Study SCI-LIDO-PK-002A included an adhesion assessment during the administration period; and
5. Study SCI-LIDO-PK-002A included skin irritation assessment after patch removal.

**Part 1 - “Lead-In”**: This part of study was performed to determine the appropriate procedures for swabbing the envelopes, liners, and skin for residual drug once patches (i.e., lidocaine patch 1.8% and Lidoderm/ Versatis) are removed. 36 healthy subjects were enrolled (12 subjects in each group) and administered 3 patches of either lidocaine patch 1.8%, Lidoderm, or Versatis for 12 hours.

- A swabbing procedure was performed to determine the amount of residual drug in the envelope, the patch liner, and the skin after patch removal (6 times per patch area for 18 total swabs per subject). Each swab was placed in a separate bag for analysis. This allowed for the determination and comparison of mass balance of residual drug from these sources in the pharmacokinetic portion of the study.
  - “Apparent dose” was determined by the total residual drug between used patches, envelopes/liners, and skin for the two patch treatments.
Immediately after application (0 hour), at each hour, and before patch removal, the patches were checked for degree of adhesion using the FDA 5-point scale and EMA 7-point scale. After patch removal, the subjects were assessed for skin irritation.

- **Part 2 “PK”**: This part of study was a single-center, randomized, crossover, comparative pharmacokinetic study. On Day -1 (Period 1) and Day 7 (Period 2), subjects were checked into the clinic site. On Day 1 (Period 1) and Day 8 (Period 2), subjects were administered either 3 lidocaine patches 1.8% or Lidoderm (dependent on each subject’s randomization scheme) for 12 hours to a defined area of normal skin on the back. All subjects completed a 7-day washout period following Period 1 and Period 2.

  - Serial PK samples were collected for the determination of lidocaine plasma concentration at (pre-dose/Time 0) and at scheduled time points up to 48 hours following the patch application. All subjects completed a 7-day washout period following Period 1 and Period 2. At the time of each pharmacokinetic blood draw, any part of the patch that was observed to be lifting was pressed down firmly (for not more than 10 seconds).

  - Patches were evaluated for degree of adhesion. They were evaluated immediately after application (0 hour), at each hour (+/- 5 min), and before patch removal. The patches were checked for degree of adhesion as outlined in Table 7.

  - Safety and tolerability were evaluated by monitoring the occurrence of AEs, local tolerability, changes in abbreviated physical examination findings, ECGs, vital signs (blood pressure and pulse rate) measurements, and clinical laboratory test results (biochemistry, hematology).

  - Skin irritation was evaluated at the site of application immediately after patch removal. Once skin irritation was assessed, all patched areas were swabbed for residual lidocaine.

See Section 5 for a discussion of the pharmacokinetic results.

**Safety Results:** The safety population for the entire study (Lead-In and Pharmacokinetic Portion) was 90 subjects. There were no deaths or SAEs. There were no AEs reported in the Lead-In Portion. In the PK Portion, one subject (1.9%) in the lidocaine patch 1.8% group and one subject in Lidoderm group experienced a single AE (facial acne and syncope, respectively) and neither resulted in study discontinuation. These AEs were mild in intensity and not considered related to study treatment. Notably, there were no severe or serious cutaneous adverse reactions. The dermal response score was either 0 (no irritation) or 1 (mild erythema, barely perceptible) for all patch assessments for both Lidoderm and lidocaine 1.8% patch. Slightly more subjects exposed to Lidoderm had maximum irritation scores of 1 (24/54 or 44%) compared to lidocaine 1.8% patch (18/54, 33.3%). However, slightly more subjects exposed to lidocaine 1.8% patch had a maximum irritation score of 2 (2/54, 3.7%) compared to Lidoderm (0/54). These two subjects had a score of 2 (definite
erythema, readily visible; or minimal edema; or minimal papular response). No patients had irritation scores greater than 2 and the Applicant notes no statistical difference between the mean irritation scores for lidocaine 1.8% patch compared to Lidoderm. Adhesion was evaluated in this study and the data were reviewed by the statistical team. The major concern with the study was not it was not blinded, which may impact the objectivity of the study. Otherwise, the sponsor’s data supported that the adhesion of the proposed produce is non-inferior to the listed drug.

Summary and Conclusion:
- When used as directed, lidocaine patch 1.8% and Lidoderm were well-tolerated with one mild AE reported for each product.
- Of note, adhesion was also compared between the two products in the study, but the study was not blinded, which may impact the objectivity of the study.

II- Study SCI-LIDO-PK-002B
Phase 1, Randomized, Comparative Pharmacokinetic Study of Lidocaine Medicated Plaster 1.8% (ZTlido™) and Lidocaine Medicated Plaster 5% (Versatis) in Healthy Subjects

This study had the same design as Study SCI-LIDO-PK-002A with exception of using Versatis instead of Lidoderm. Versatis is an approved drug product in the European Union (EU). The study subjects who completed Study SCI-LIDO-PK-002A were re-randomized and rolled over into Study SCI-LIDO-PK-002B after a 7-day washout period. The Applicant planned to enroll all 54 subjects in the PK Portion, but 53 subjects were enrolled and completed the study. Thus, the safety population for this study was 53 subjects.

Safety Results: A total of 8 AEs occurred among 6 subjects. Five of the AEs (4 subjects) were observed for the lidocaine medicated plaster 1.8% treatment and 3 AEs (2 subjects) were observed for the Versatis treatment. There were no SAEs. All AEs were considered treatment related and mild in severity. The AEs observed for lidocaine medicated plaster 1.8% were hemoglobin decrease (1), arthralgia (1), headache (1), oropharyngeal pain (1), and erythema (1). The AEs observed for Versatis were alanine aminotransferase increase (1), aspartate aminotransferase increase (1), and rash (1). All the AEs were mild.

Summary and conclusion:
In a small study, lidocaine medicated plaster 1.8% and Versatis were well-tolerated, without severe skin reactions. Of note, adhesion was assessed in this study, but is not reviewed given that the comparator was a product approved in the EU.

III- Study SCI-LIDO-ADH-001 (A15.0168)
An Open Label, Single-Treatment, Single-Period, Single-Application, Adhesion Performance Study of Lidocaine Patch 1.8% in Healthy Adults

Objectives:
- **Primary**: To evaluate the adhesion performance of ZTlido
- **Secondary**: To monitor AEs and safety
N: 54 healthy subjects (≥ 18 years)

**Treatment:** 3 lidocaine patches 1.8%

**Duration of Study:** 1 day

**Duration of exposure to Lidocaine patch 1.8%:** 12 hour

**Design:** An open label, single-treatment, single-period, single-application, adhesion performance study in healthy, adult, human subjects

**Endpoints:**

**Primary endpoint of adhesion:** The Cumulative Adhesion Score (CAS) was the primary endpoint and was defined as the sum of adhesion scores at 0 hour (right after patch application), 3, 6, 9, and 12 hours (after patch application). The mean CAS (i.e. score obtained by dividing the CAS with total number of observations) was also provided.

**Assessment:**
- Adhesion assessment after application (0 hour) and at 3, 6, 9, and 12 hours
- Safety assessment (physical exam, vital signs, ECG, labs) at the time of check-in and throughout the study
- Skin irritation assessment at pre-application (0 hour), 30 minutes post patch removal, and at 2 hours post patch removal

Adhesion was graded using a standard scale (Table 7).

<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>≥ 90% adhered (essentially no lift off the skin)</td>
</tr>
<tr>
<td>1</td>
<td>≥ 75% to &lt; 90% adhered (some edges lifting off the skin)</td>
</tr>
<tr>
<td>2</td>
<td>≥ 50% to &lt; 75% adhered (less than half of the patch lifting off the skin)</td>
</tr>
<tr>
<td>3</td>
<td>&gt; 0% to &lt; 50% adhered but not detached (more than half of the patch lifting off the skin without falling off)</td>
</tr>
<tr>
<td>4</td>
<td>0% adhered (patch completely off the skin)</td>
</tr>
</tbody>
</table>

Source: Study A150188, Complete Study Report, Page 66, submitted 8/28/17

**Results and Discussion:** As noted in Section 3, a consult was made to the Division of Biometrics VI (DB-VI), Office of Biostatistics to evaluate the Applicant’s adhesion data of ZTlido in this study.

The Division of Biometrics VI, Office of Biostatistics (DB-VI) noted that while the Applicant used the (CAS) during the 12-hour application period as the primary endpoint of adhesion, the CAS is not meaningful in determining adhesion since different combination of adhesion scores...
could yield the same CAS. While DB-VI disagreed with this endpoint, and disagreed with the Applicant’s statement that “greater than 90% of subjects had ≥ 90% adhesion” DB-VI analyses showed that ZTlido met the adhesion criteria.

**Safety Results:** No adverse events were reported in this study. No patches were removed early for unacceptable irritation and no subject dropped out of the study.

**Conclusion:** The adhesion data supported that ZTlido passes the adhesion criteria.

### IV- Study SCI-LIDO-HEX-001 (A15.0188)

An Open-Label, Randomized, Three-Treatment, Three-Sequence, Three-Period, Cross-over, Pharmacokinetic and Adhesion Performance Study of Lidocaine Patch 1.8% (36 mg) (3 patches) in Fasting, Healthy, Adult Human Subjects with Physical Exercise, Heat, and Normal Conditions

**Objectives:**
- Primary: To evaluate the PK and adhesion performance of ZTlido (× 3 patches) under fasting with physical exercise, heat, and normal conditions
- Secondary: To monitor the AEs and to ensure the safety of the subjects

**Cohorts:**
- Treatment A: Lidocaine patch 1.8% with physical exercise (bike for 30 minute immediately after patch application and at 2.50, 5.50, and 8.50 hours post-patch application)
- Treatment B: Lidocaine patch 1.8% with heat (standard heating pad at medium setting for 20 minutes immediately after patch application and at 8.50 hours post-application; a blanket/towel was placed between the patches and heating pad to reduce the chance of skin burning)
- Treatment C: Lidocaine patch 1.8% normal condition

N: 12 healthy subjects

**Treatment:** 3 lidocaine patches 1.8%

**Duration of Study:** 2.5 weeks (12 hours for each treatment with 7-day washout)

**Duration of exposure to Lidocaine patch 1.8%:** 12 hour for each treatment

**Key Inclusion and Exclusion Criteria:** Healthy subjects 18 years of age and older

**Design:** Twelve healthy subjects were randomized to 3 groups of Treatment A (physical exercise), Treatment B (heat), and Treatment C (normal) during three separate periods. For each treatment period, subjects were admitted to the study site at least 12 hours before patch application, and remained on site for 24 hours post-application. During this time, three lidocaine patches 1.8% were applied to the mid-
lower back and worn for 12 hours. Blood samples for the determination of lidocaine plasma concentrations were collected before the application of lidocaine patch (predose) and then in a serial manner at scheduled time points up to 48 hours after application of the lidocaine patches. No tape or overlay was used to reinforce patch adhesion. A 7-day washout period was maintained between each treatment period.

During Treatment A, subjects exercised on a bike for 30 minutes (target heart rate: 108 bpm) immediately after patch application and at 2.5, 5.5, and 8.5 hours post-patch application with window period of ± 10 minutes. During Treatment B, a standard 3-setting heating pad used in accordance with the manufacturer’s instructions at a medium setting for 20 minutes immediately after patch application and at 8.5 hours post-application. A blanket/towel was placed between the patches and heating pad to reduce the chance of skin burning. Subjects did not exercise or apply a heating pad during Treatment C (normal conditions).

Safety Assessment: Detailed medical examination including medical history, physical examination, vital signs, clinical laboratory tests, and 12-lead ECG were carried out at the time of screening to exclude any clinically significant medical condition that may interfere or likely to interfere with the pharmacokinetics of the drug. Safety assessments were carried out at the time of check-in and throughout the study.

Vital signs monitoring (blood pressure, pulse rate, and respiratory rate) were conducted before patch application and at 4, 10, and 24 hours after patch application. A Subject Well Being Questionnaire (SWBQ) was done before patch application and at 4, 10, and 24 hours post-patch application and at the ambulatory visit.

Skin Irritation Assessment: Skin irritation was evaluated at the site of application: at Pre-application (0 hour) [within 30 minutes before patch application], 30 minutes (with a window period ±10 minutes) post patch removal, and at 2 hours post-patch removal with a window period of ±15 minutes.

Adhesion Assessment: Adhesion assessment was done immediately after application (0 hour) and at 0.5, 3, 6, 9, and 12 (before patch removal) hours after application. The patch adhesion scale is in Table 7.

For each subject, the adhesion scores for each treatment (A, B, and C) at each time point were calculated as average of 3 patches. The primary endpoint of adhesion was the Cumulative Adhesion Score (CAS) during the 12-hour application period (i.e. the CAS for a specific subject was the sum of the adhesion scores recorded immediately after the patch has been applied (0 hour) +3, +6, +9, and +12 hours after application). See the discussion for study SCI-LIDO-ADH-001 regarding limitations of the CAS endpoint.

Adhesion results: Adhesion analysis included all patches from 12 subjects and no patches fell off during the study or were removed early for unacceptable irritation or
dropped out of the study before the end of the 12-hour application. The cumulative adhesion score and mean adhesion score for Treatments A, B, and C, are summarized in Table 8.

Table 8: Summary Statistics of Adhesion Performance of Lidocaine Patch 1.8% with Physical Exercise, Heat, and Normal Conditions

<table>
<thead>
<tr>
<th>Statistics</th>
<th>Treatment*</th>
<th>N</th>
<th>Minimum</th>
<th>Maximum</th>
<th>Mean</th>
<th>S.D.</th>
<th>CV (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cumulative Adhesion Score</td>
<td>A</td>
<td>12</td>
<td>0</td>
<td>5</td>
<td>2.00</td>
<td>2.335</td>
<td>116.8</td>
</tr>
<tr>
<td></td>
<td>B</td>
<td>12</td>
<td>0</td>
<td>2</td>
<td>0.42</td>
<td>0.793</td>
<td>190.3</td>
</tr>
<tr>
<td></td>
<td>C</td>
<td>12</td>
<td>0</td>
<td>0</td>
<td>0.00</td>
<td>0.000</td>
<td>-</td>
</tr>
<tr>
<td>Mean Adhesion Score</td>
<td>A</td>
<td>12</td>
<td>0</td>
<td>1</td>
<td>0.33</td>
<td>0.389</td>
<td>116.8</td>
</tr>
<tr>
<td></td>
<td>B</td>
<td>12</td>
<td>0</td>
<td>0</td>
<td>0.07</td>
<td>0.132</td>
<td>190.3</td>
</tr>
<tr>
<td></td>
<td>C</td>
<td>12</td>
<td>0</td>
<td>0</td>
<td>0.00</td>
<td>0.000</td>
<td>-</td>
</tr>
</tbody>
</table>

* Treatment: A: With Physical exercise B: With Heating & C: Under Normal conditions

Source: Table 6 from Study SCI-LIDO-HEX-001

There was no level of detachment (i.e., score 0) observed for any subject under normal and heat conditions (B and C). Slight lifting at corners and edges were observed for some patches during exercise periods (Scores of 1 and 2), which was attributed to sweat excretion under the patch. However, the patches were observed to re-adhere after the skin dried with adhesion scores of 0 at subsequent time points. No subjects experienced what the Applicant defined as a meaningful degree of detachment (i.e., score ≥ 3).

Safety Results: No serious adverse events were reported. All the study subjects completed the study. A total of 6 AEs were reported in 4 subjects (33.3% of subjects) including headache (3), light headedness secondary to exercise (1), menstrual cramps (1), and head cold (1). Minimal dermal irritation at the patch application site was observed during the study (mean score < 1, where 1 = minimal erythema, barely perceptible irritation). Most subjects had a dermal irritation score of 0 (no evidence of irritation).

Pharmacokinetic results: See section 5.

Summary and conclusion:
- No safety signals were detected in this PK study.

INTEGRATED SAFETY SUMMARY

In the clinical program, there were a total of eight studies in which 508 subjects were exposed to lidocaine patch 1.8%, 429 subjects were exposed to Lidoderm 5% patch, 58 subjects were exposed to IV lidocaine (7mg/kg), and 65 subjects were exposed to Lidocaine Medicated Plaster 5% (Versatis). The occurrence of overall AEs is summarized by study in Table 9.
The numbers of subjects with AEs by most affected System Organ Class (SOC) are shown in Table 10 for each study regardless of the treatment applied. In general, there was no pattern to the adverse event SOCs. AEs related to skin and subcutaneous disorders were expected given the method of treatment application.
Table 10: Analysis of Adverse Events by System Organ Class for the Safety Population of Each Study

<table>
<thead>
<tr>
<th></th>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Nervous system disorders</td>
<td>5</td>
<td>0</td>
<td>0</td>
<td>3</td>
<td>0</td>
<td>4</td>
<td>1</td>
<td>1</td>
<td>17</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>8</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>8</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>4</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>9</td>
</tr>
<tr>
<td>Injury, poisoning, and procedural complications</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>4</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>6</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>4</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>6</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>Infections and infestations</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>4</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Reproductive system and breast disorders</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Laboratory evaluations</td>
<td>2</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>Totals</td>
<td>20 (27.5%)</td>
<td>3 (5.0%)</td>
<td>1 (1.4%)</td>
<td>24 (9.7%)</td>
<td>0 (0.0%)</td>
<td>6 (5.0%)</td>
<td>2 (3.7%)</td>
<td>8 (14.8%)</td>
<td>64 (12.0%)</td>
</tr>
</tbody>
</table>

* The same subjects were enrolled in SCI-LIDO-PK-002A and SCI-LIDO-PK-002B. The studies were conducted sequentially separated by a 7-day washout period and re-randomization. ND = Not done

Source: Summary of Clinical Safety, Table 2.7.4.14, page 35, submitted 8/28/17

There were no deaths or serious adverse events in any of the studies. The initial NDA submission included safety data from studies SCI-LIDO-PK-001, SCI-LIDO-DERM-001, SCI-LIDO-PHOTO-001, and SCI-LIDO-PHOTO-002. In the current complete response submission, data from healthy subjects are included for studies SCI-LIDO-PK-002A, SCI-LIDO-PK-002B, SCI-LIDO-ADH-001, and SCI-LIDO-HEX-001. The previous studies included three cases of severe AEs and seven cases of discontinuation of study medication. These were reviewed in detail during the initial submission and during the resubmission as discussed above. The three cases of severe AEs (skin erosion, blister, and erythema/bullae) for ZTlido occurred in Study SCI-LIDO-DERM-001. This study was performed to evaluate potential sensitization and skin irritation in a repeat insult patch test (RIPT) setting. The severe skin reaction in these cases might have been due to prolonged exposure to the patches for a 48-hour period. In the current studies, there are no reports of severe skin irritation or any other significant dermal safety concerns when the patches were used for 12 hours, which is the appropriate duration of patch application as noted in the proposed label.

In the entire clinical program, there were seven discontinuations of study medication due to an adverse event, including five cases in Study SCI-LIDO-DERM-001 [skin blister, skin erythema/bullae, mild Herpes zoster (shingles), moderate erythema (erythematous eczematous) on back and abdomen, and moderate chest discomfort (chest tightness)], 1 case in Study SCI-
LIDO-PK-001 (contact dermatitis at baseline that worsened 12 h after IV lidocaine), and 1 case in Study SCI-LIDO-PHOTO-001 [photosensitivity reaction (photo-dermatitis)].

It was noted in review of Study SCI-LIDO-DERM-001 that there were more cases of skin irritation with ZTlido compared to Lidoderm under exaggerated conditions when the patches were worn for a 48-hour period. DDDP recommended that potential for severe skin irritation should be added to labeling. Labeling negotiations are ongoing with the Applicant, but the draft label includes information regarding the risk or skin irritation. Data from studies SCI-LIDO-PHOTO-001 and SCI-LIDO-PHOTO-002 suggest that ZTlido is not photoallergic or phototoxic.

The studies of ZTlido were performed in healthy subjects at least 18 years old. In the current studies, there were no geriatric subjects. In the initial submission, there were 13 subjects who were older than 70 years. Safety assessments by age were considered during the previous review cycle and the conclusion was made that the available data provide some relevant experience in geriatrics.

Overall, it appears that based on the safety data in healthy volunteers, the safety profile of ZTlido is that expected for a topical lidocaine patch. There are limited comparative data for ZTlido and Lidoderm, but there were more severe skin related AEs for ZTlido than for Lidoderm under exaggerated conditions of prolonged use.

The lidocaine patch 1.8% (ZTlido) has been developed to be bioequivalent to Lidoderm, but with improved drug delivery compared to Lidoderm. The improvement in drug delivery allows for ZTlido to be compounded with 36 mg of lidocaine, versus 700 mg of lidocaine with the Lidoderm Patch 5%. Thus, the amount of lidocaine in the patches is lower and the amount of residual lidocaine is lower, which is notable given the potential safety risks associated with accidental patch exposures.

**Adhesion**
The previous data failed to provide adequate evidence to support the adhesion of ZTlido because patches were used for 48 hours rather than the intended 12-hour use. In the current submission, there are adequate data from study SCI-LIDO-ADH-001 from 12 hours of use to support product adhesion.

**9. Advisory Committee Meeting**
No issues were identified in these submissions that warranted advisory committee discussion. Therefore, no advisory committee meeting was convened.

**10. Pediatrics**
- **Peds exclusivity board review** – PPSR/WR – Not applicable
• **PeRC Review Outcome**—PMCs, deferrals, waivers, pediatric plan, peds assessment

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable. As none of these considerations applied, the application did not trigger PREA. In addition, the low incidence of PHN in the pediatric population makes studies in this population infeasible.

11. **Other Relevant Regulatory Issues**

• **Application Integrity Policy (AIP)**—Not applicable.

• **Exclusivity or patent issues or concern**—Scilex provided patent certification for the listed drug Lidoderm (NDA 020612). In the original application, the annotated label provided by the Applicant included reference to however the NDA did not contain a patent certification or statement with respect to each patent listed in FDA’s Orange Book for In this complete response, Scilex removed reference to

• **Financial disclosures**—No issues.

• **Other GCP issues**—No issues.

• **Office of Scientific Investigation (OSI) audits**—The Office of Study Integrity and Surveillance (OSIS) conducted an inspection of study SCI-LIDO-PK-002A from A form FDA 48 was issued at the inspection close-out. The final inspection classification is Voluntary Action Indicated (VAI). See the form 483 for a list of the observations. After review of the firm’s responses the major recommendation was accepting data from SCI-LIDO-PK-002 Initially, there were also concerns with the lidocaine residual study, but the firm adequately addressed these concerns.

• **Other outstanding regulatory issues**—None

12. **Labeling**

• **Proprietary name**—The proposed proprietary name, ZTlido, was reviewed by the Division of Medication Error and Prevention and Analysis and found to be conditionally acceptable.

• **Physician labeling**
The labeling for ZTlido is the first instance of Prescribing Information (PI) in Physicians Labeling Rule (PLR) format for a lidocaine topical system product. One lidocaine patch (Lidoderm 5%) is approved in non-PLR format. Lidoderm is indicated for relief of pain associated with post-herpetic neuralgia (PHN).

In the current application, the Applicant submitted proposed labeling similar to the listed drug (NDA 20612, Lidoderm), but modified to conform to the PLR format. In addition, the labeling has updates based on the scientific literature and with data specific to this product.

The Office of Policy for Pharmaceutical Quality (OPPQ) was consulted to assist with labeling ZTlido (lidocaine topical system) 1.8% due to policy considerations related to the presentation of the strength. Specifically, despite the differences in strength between ZTlido 1.8% and Lidoderm 5%, they are equivalent in terms of providing the same amount of lidocaine systemic exposure. The review team was concerned that this is a safety issue as providers and patients may be confused and think that ZTlido 1.8% provides less systemic exposure to lidocaine than Lidoderm 5%. This confusion could lead to safety concerns and the review team recommended that the labeling include a statement regarding the equivalency of lidocaine systemic exposure for the two products. OPPQ initially noted that issues of equivalency are typically included in labeling when they warn that two products are not equivalent or cannot be substituted. However, after discussion of the safety concerns, OPPQ agreed that a statement was necessary to avoid confusion. OPPQ was consulted for feedback regarding the type of statement (phrasing as well as location) given that this is a policy issue.

After discussion with OPPQ and the entire review team, there was agreement to add the following equivalency statement:

One ZTlido (lidocaine topical system) 1.8% provides equivalent lidocaine exposure to one Lidoderm® (lidocaine patch 5%).

In the labeling, this equivalency statement will be included in the highlights (dosage and administration), Section 2.1 (Dosage and Administration), Section 12.3 (Clinical Pharmacology), the cartoon, and the container.

In the dosage and administration section, text was added to note that because of the difference in bioavailability of ZTlido compared to Lidoderm 5% a different dosage strength is required to be administered to the patient.

Another major discussion point during labeling was introduction of the new dosage form term “topical system.” OPPQ recommended topical system be used throughout the labeling except where specifically referencing Lidoderm, which has the dosage form term “patch.” In addition, OPPQ recommended use of topical system throughout the patient labeling.

A summary of other major labeling considerations is included below:
1) Indications and usage—Consistent with Lidoderm, the proposed indication is for relief of pain associated with post-herpetic neuralgia (PHN).

2) Dosage and Administration—In addition to adding the equivalency statement discussed above, the section was divided into Important Dosage and Administration Instructions and Post-herpetic Neuralgia.

3) Contraindications—No changes

4) Warnings and Precautions: The Warnings and Precautions were revised to be consistent with the Guidance on labeling for this section\(^1\). Per the guidance, each adverse reaction, syndrome, or group of reactions with a common pathogenesis included in Warnings and Precautions section should have its own numbered subsection. The subsection title should accurately characterize the risk.

5) Adverse Reactions section: This section was updated to be consistent with current labeling practice in terms of format and content.

6) Use in Specific Populations: This is the first lidocaine patch label to undergo Pregnancy and Lactation Labeling Rule (PLLR) formatting. The section was revised based on PLLR regulations and guidance. The Applicant submitted literature references to support the proposed PLLR changes. For the non-clinical information, 8 studies were identified via an adequate search of relevant databases and the articles were submitted to the NDA and reviewed by the pharmacology toxicology team. Please see the pharmacology toxicology review for additional details of the review.

For the clinical changes, the Applicant added literature reference from two studies by Abboud et al. (1982\(^2\) and 1983\(^3\)). Abboud et al. studied neonates of 22 parturient women for the effects of epidural 1.5% lidocaine anesthesia vs. a control group of neonates whose mothers received no analgesics, medications, or local anesthetics for labor or delivery. Based on these studies, Abboud et al. concluded that lidocaine epidural anesthesia has no significant effect on the baseline fetal heart rate, uterine activity, or early neurobehavioral status of the neonate.

The Applicant also provided literature reference to the three following studies regarding the safety of lidocaine during lactation. Ortega et al (1999\(^4\)) followed 25 women who received epidural 2% lidocaine and 0.5% bupivacaine anesthesia for adverse reactions

related to the excretion of local anesthetics into breast milk. Ortega et al. concluded that the use of both lidocaine and bupivacaine for epidural anesthesia is safe with regard to breast-feeding. Giuliani et al (2001^5) studied the effect of 2% lidocaine as an anesthetic during dental procedures and concluded that nursing mothers can safely continue breastfeeding if they receive lidocaine local anesthesia for a dental procedure. The third study provided by the Applicant was a case report from Lebedevs et al (1993^6). This case report presented a nursing woman who received local lignocaine for a dental procedure and the ratio of Lignocaine and its primary metabolite were studied in milk and plasma. Lebedevs et al. concluded that except for very rare allergic reactions, levels of infant exposure are extremely low and of no toxicological significance.

The articles described above provided reasonable clinical evidence to support the suggested PLLR labeling for ZTlido. The labeling was updated to conform to PLLR format requirements.

7) Pharmacokinetics—This section was revised to include information from study SCI-LIDO-PK-002A since this was the pivotal bioavailability study that bridged ZTlido to Lidoderm.

8) Clinical Studies—Data regarding the adhesion study were included in this section of the labeling and modified to reflect adhesion during the 12 hour application period.

- **Highlight major issues that were discussed, resolved, or not resolved at the time of completion of the CDTL review**

As discussed above. The proposed package insert was reviewed by the Office of Prescription Drug Promotion (OPDP) and changes were recommended.

Labeling negotiations are ongoing with the Applicant at the time of this review.

- **Carton and immediate container labels (if problems are noted)**

The labeling was reviewed by DMEPA and recommended changes were incorporated.

- **Patient labeling/Medication guide (if considered or required)**

The Division of Medical Policy Programs (DMPP) reviewed the PPI and IFU and provided recommendations that will be incorporated into labeling.

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9) Recommendations/Risk Benefit Assessment

- **Recommended Regulatory Action**

We recommend approval of this NDA for ZTlido for relief of pain associated with post-herpetic neuralgia (PHN).

- **Risk Benefit Assessment**

The risk-benefit profile is favorable of ZTlido for relief of pain associated with post-herpetic neuralgia (PHN). The Applicant has established an adequate pharmacokinetic bridge to Lidoderm and is relying on the Agency’s previous findings for efficacy and safety for Lidoderm. In addition, the Applicant has provided adequate data to support dermal safety and adhesion.

- **Recommendations for Postmarketing Risk Evaluation and Management Strategies**

A Risk Evaluation and Management Strategy (REMS) is not recommended for this product.

- **Recommendation for other Postmarketing Requirements and Commitments**

The non-clinical team has recommended the following PMRs:

1. Conduct a 9-month minipig study using the to-be-marketed drug product. The study should mimic the clinical use of the drug product with repeated applications to the same location as per the product labeling.

2. Conduct a 2-year dermal carcinogenicity study to evaluate the carcinogenic potential of terpene resin, dipropylene glycol, SIS block copolymer, isostearic acid, and polyisobutylene.

3. Conduct an Ames assay or provide adequate data based on validated analytical methods that the levels of this compound that can leach from the patches at the maximum daily dose (3 patches per day) remain below 10 mcg/day.

- **Recommended comments to applicant**

None
Deputy Director Comment
I concur with Drs. Haghpanah and Maynard’s recommendation for approval of this application. The risk/benefit assessment favors approval for this product for the proposed indication. I also concur with the nonclinical post marketing requirements.
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SEPIDEH HAGHPANAH
02/28/2018

JANET W MAYNARD
02/28/2018

ELLEN W FIELDS
02/28/2018

Reference ID: 4227523