

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-504

APPROVAL LETTER(S)



NDA 21-504

Vyteris, Inc.
13-01 Pollitt Drive
Fair Lawn, NJ 07410

Attention: George M. Baskinger
Manager, Quality Management and Regulatory Compliance

Dear Mr. Baskinger:

Please refer to your new drug application (NDA) dated September 25, 2002, received September 25, 2002, and submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, for LidoSite™ Topical System comprised of the LidoSite™ Patch (Lidocaine HCl / Epinephrine topical iontophoretic patch) 10%/0.1% and the LidoSite™ Controller.

We acknowledge receipt of your submissions dated May 9, June 4 and 21, July 8, August 26, and December 18, 2002, February 26, March 10, 11 (2), 19, and 31, April 29, May 1, 15 (2), and 27, June 5, 13(2), 16, 20, 24, and 28, July 14(2), 15, and 18 (2), August 1, 8 and 20, September 8, November 8, 18, 21, 25, and 26, 2003, and January 30, March 18, 27, and 31, April 2, 5, 24, and 28, and May 3, 4 and 6, 2004.

The November 8, 2003, submission constituted a complete response to our July 25, 2003, action letter.

This new drug application provides for the use of LidoSite™ Topical System as a topical local anesthetic delivery system indicated for use on normal intact skin to provide local analgesia for superficial dermatological procedures such as venipuncture, intravenous cannulation, and laser ablation of superficial skin lesions, on patients 5 years of age and older.

We have completed our review of this application, as amended, and it is approved, effective on the date of this letter, for use as recommended in the attached labeling (package insert), with the following minor revisions listed below and the labeling submitted April 24, 2004 (controller carton, supplemental controller carton and controller label) and April 28, 2004 (pouch primary, pouch patch carton, supplemental pouch patch carton labels and printed patch film).

1. On the Instruction Sheet:
 - a. Change Item 3h from "the application site may not be fully anesthetized" to "the medication may not have been delivered to the application site."
 - b. Change the footer of the instruction sheet from "Each patch contains Lidocaine HCl (10%), Epinephrine (0.1%)" to "Lidocaine HCl/Epinephrine topical iontophoretic patch 10%/0.1%."

2. Include the NDC number in the HOW SUPPLIED section of the package insert and on the immediate carton and container labels.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert), and the labeling submitted April 24, 2004 (controller carton, supplemental controller carton and controller label) and April 28, 2004 (pouch primary, pouch patch carton, supplemental pouch patch carton labels and printed patch film). Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit the copies of final printed labeling (FPL) electronically, according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format – NDA*. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved NDA 21-504." Approval of this submission by FDA is not required before the labeling is used.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We are deferring submission of your pediatric studies for ages 0 to 5 years until November 2007.

Your deferred pediatric studies required under section 2 of the Pediatric Research Equity Act (PREA) are considered required postmarketing study commitments. The status of this postmarketing study shall be reported annually according to 21 CFR 314.81. This commitment is listed below.

POST MARKETING COMMITMENT

1. Deferred pediatric study under PREA for the indication of local analgesia for superficial dermatological procedures such as venipuncture, intravenous cannulation, and laser ablation of superficial skin lesions in pediatric patients ages birth to 5 years.

Final Report Submission: April 2007

Submit final study reports to this NDA. For administrative purposes, all submissions related to this pediatric postmarketing study commitment must be clearly designated "**Required Pediatric Study Commitment.**"

Submit clinical protocols to your IND for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all study final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii), you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies, number of patients entered into each study. All submissions, including supplements, relating to these postmarketing study commitments must be prominently labeled "Postmarketing Study Protocol," "Postmarketing Study Final Report," or "Postmarketing Study Correspondence."

We also remind you of your agreements to the following:

1. Accrual of data for commercial batches of drug product for the cathode and anode probe tack, the apparent compressive modulus of the reservoirs (electrodes), the probe tack of the adhesive, and the anode-specific and cathode-specific conductivities with data based on eight lots of subcomponents.
2. Development, validation, and establishment of an *in-vitro* drug release test method as part of the drug product specifications. The method will be submitted as a Prior Approval Supplement within eighteen months from the date of the action letter.

In addition, submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to this division and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising,
and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Please submit one market package of the drug product when it is available.

We have not completed validation of the regulatory methods. However, we expect your continued cooperation to resolve any problems that may be identified.

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Kimberly Compton, Regulatory Project Manager, at (301) 827-7432.

Sincerely,

{See appended electronic signature page}

Bob Rappaport, M.D.
Director
Division of Anesthetic, Critical Care and
Addiction Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-504

APPROVABLE LETTER(S)



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-504

Vyteris, Inc.
13-01 Pollitt Drive
Fair Lawn, NJ 07410

Attention: George M. Baskinger
Manager, Quality Management and Regulatory Compliance

Dear Mr. Baskinger:

Please refer to your new drug application (NDA) dated September 25, 2002, received September 25, 2002, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for LidoSite Lidocaine Iontophoretic (lidocaine HCl and epinephrine bitartrate) Drug Delivery System.

We acknowledge receipt of your submissions dated May 9, June 4, and 21, July 8, August 26, and December 18, 2002, February 26, March 10, 11 (2), 19, and 31, April 29, May 1, 15 (2), and 27, June 5, 13 (2), 16, 20, and 24, 2003.

We also acknowledge receipt of your submissions dated June 28, July 14 (2), 15, and 18 (3), 2003. These submissions were not reviewed for this action. You may incorporate this submission by specific reference as part of your response to the deficiencies cited in this letter.

Our field investigator could not complete inspection of the LidoSite patch manufacturing facility at Vyteris, Inc., 13-01 Pollitt Drive, Fair Lawn, New Jersey because the facility was not ready for inspection. A satisfactory inspection of all the manufacturing facilities is required before this application may be approved.

We have completed our review of this application, as amended, and it is approvable. Before the application may be approved, however, it will be necessary for you to address the following deficiencies.

1. Provide an explanation for the high incidence of high skin impedance in study 98NS-01-10.
2. Provide an explanation for the high incidence of papular rash in study BDTS-00-57.
3. Provide an explanation for defining burns as a Draize erythema score of 4 (a serious adverse event by your definition), but then reporting no serious adverse events despite multiple reports of burns, including at least one 2nd degree burn, related to use of the patch.

4. Provide an accounting for skin reactions not previously reported as AE's, e.g., in study 98NS-01-09, subject 915 had burns at all four application sites and subject 923 had skin removed by the patch adhesive at all four application sites per the DERMAL dataset, yet the adverse events dataset (ADVRE) contained none of these events.
5. Retabulate the adverse events tables to include the points below as to allow for more appropriate product labeling.
 - a. Pain: Retabulate AE's to include all pain in one category with subcategories to include "pain NOS" and all unpleasant sensory AE's such as "application site burning" unless justification is provided otherwise. Resolve these events into those temporally associated with patch application, patch removal, procedure, post-procedure.
 - b. Burns: Justify creation of a separate "burns NOS" category and define entry to this category. Retabulate AE's to include all burns in one category with subcategories to include burns NOS.
 - c. All skin reactions: Present a tabulation of all skin reactions, with subcategories including rashes, erythema, burns, pallor/blanching, hematoma, sunburn, dermatitis, pruritis, etc.
 - d. Placebo groups: retabulate integrated AE tables to with separate incidence columns for "passive" placebos (i.e., no current) and for "active" placebos (with current).
 - e. Provide a comprehensive tabulation of adverse events for all studies of MIP II and III
6. DMI _____) and DMF _____) were deemed inadequate to support your NDA. Deficiency letters were sent to the respective DMF holders.
7. Provide acceptance specifications for lidocaine hydrochloride and epinephrine bitartrate.
8. Provide a revised specification for glycerin, USP by including the revised USP specification for the purity, described in USP 25 as follows:
 - a. Not more than 0.1% if any individual impurity, excluding diethylene glycol
 - b. Not more than 1.0% of total impurities, including diethylene glycol
9. Provide the detailed manufacturing procedure of the electrode subassembly since it is a critical component of the patch. Alternatively, provide a reference to a drug master file (or device master file) from its vendor.
10. Provide a description of the sampling procedures (number sampled, frequency and location of sampling, etc.) for the in-process tests described in the manufacture of the patches and explain how the critical visual tests are validated to minimize human errors.
11. Provide revised drug product specifications containing the following:
 - a. Individual unspecified and unidentified degradation products of lidocaine: NMT _____ or _____ TDI whichever is lower.

- b. Individual unspecified and unidentified degradation products of epinephrine: NMT _____, or _____ whichever is lower.
 - c. Qualification data for the degradation products of lidocaine exceeding _____ or _____ whichever is lower.
 - d. Qualification data for the degradation products of epinephrine exceeding _____ or _____ whichever is lower.
 - e. Tighten the acceptance criteria for probe tack and apparent compressive modulus for both cathode and anode, the pH of hydrogel surface for cathode reservoir, and patch probe tack (peripheral adhesive), and include lower and upper limits for the individuals and the averages.
12. Provide justification for the acceptance criteria for each of the electrical and electrochemical tests of the drug product, e.g., based on the pivotal clinical experience.
13. Provide a drug release test (*in vitro* or *in vivo*) to measure the product performance e.g., using _____ In the absence of such a test note the following:
- a. The freeze thaw studies do not adequately ensure the product performance if it freezes. Therefore, a temperature warning statement is warranted in the labeling.
 - b. The shelf life would have to be limited until the product performance over stability can be demonstrated by the drug release test method.
 - c. Some post-approval changes would also have to be restricted until sameness can be demonstrated by a product performance test.
14. As committed to in your submission dated May 27, 2003, provide stability updates for the three primary stability batches (0171001, 0172002, and 0173003) including complete statistical analyses of the data in support of the proposed expiration-dating period. The analyses should include all attributes showing stability trends, e.g., assays for lidocaine and epinephrine and their degradation products, preservative assay, trace conductance of anode and cathode, and patch probe tack (peripheral adhesive). The analyses should be based on updated acceptance criteria consistent with Agency recommendations.
15. Stability data submitted indicate that _____ Provide an explanation for the observed trends and an assessment of their impact on the product quality and performance.
16. Provide a revised stability protocol for the first three commitment batches indicating full testing of all stability parameters. Comments on the marketed stability protocol for the annual batches are withheld until the complete evaluation of the primary stability data.
17. As stated in your response to the Information Request (IR) letter dated May 2, 2003, provide data on the electrochemical stability (assay and degradation products) of the drug product (in-use stability data) during the ten-minute patient use period.

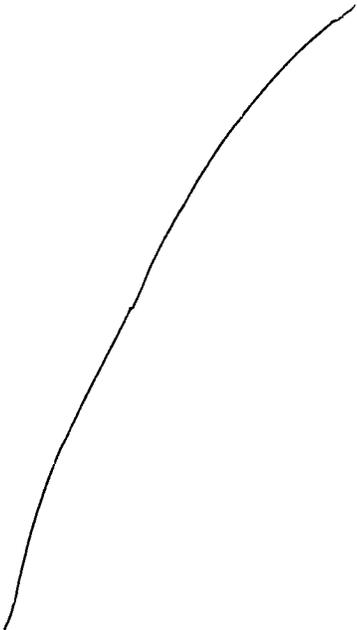
18. In view of the solubility threshold of lidocaine HCl and the presence of nearly — glycerin in the anode formulation, it is expected that lidocaine HCl, despite being freely soluble in water, may — . Provide data on the physical nature of lidocaine HCl in the patch at lower temperatures.
19. Provide data on the relative humidity (RH) versus moisture absorption isotherms for the drug product. Analysis of this data should support the choice of RH stability test condition for the drug product.
20. Provide stability data on the — of the patches. It is not clear from the data whether — is a critical stability issue that affects product performance.
21. Provide data indicating whether there is a correlation between the age, batch number, etc., of the patches used in the Phase III studies versus (i) skin peeling and (ii) instances of high impedance leading to patient withdrawal, and (c) cases of inadequate patient anesthesia. Also provide an evaluation of the potential relationship of patch probe tack test results to patient skin peeling and of trace conductance test results to patient withdrawal due to high impedance.
22. Provide a revised stability protocol for the electrode solutions with an additional testing at — since the hold time has been identified as — based on the data from —
23. Expiration dating should be computed from the date the drug substance (s) is (are) mixed with other components regardless of when the finished dosage form is prepared. Therefore, provide an amended stability protocol stating that the expiration will be computed from the date the drug substance (s) is (are) mixed with other ingredients.
24. In view of the revisions to be made in acceptance criteria and the incomplete statistical analysis of all stability-indicating test results, the comments on the proposed expiration dating period for the drug product are withheld pending the submission and review of updated stability data.
25. In the absence of a reliable *in vitro* drug release method, the attributes presently tested are insufficient to demonstrate the product performance during the temperature cycling studies reported in the NDA. Therefore, provide a warning statement in the labeling (package insert. — that the patch should not be subjected to freezing temperatures.
26. Your application states that bioequivalence requirements were waived. Provide information on this waiver and against which product requirements were waived.

In addition, it will be necessary for you to submit a draft package insert and patch, pouch, carton, and container labels modified to reflect the following comments, and the revisions noted in the attached draft label. Further labeling comments will be provided once the aforementioned deficiencies are adequately addressed.

27. The following are general Comments.

- a. The proprietary name LidoSite 
- b. The NDC number appears in a different location throughout the labeling. Relocate the NDC number to the upper right hand corner, so it does not interfere with any text on the label.
- c. You refer to the system as  on the container label and carton labeling

28. Provide revised patch and pouch/carton labels as listed below.

29. 

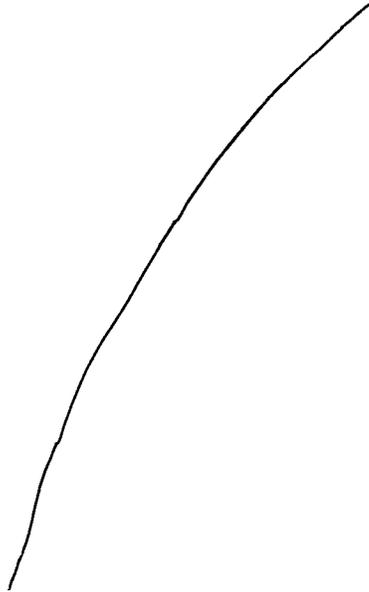
30.

31. Revise the storage statement in the package insert to read "Store at controlled room temperature [See USP] of 20° to 25°C (68° to 77°F).

32. Pouch Primary Package Label

33.

34.



You are reminded of your commitment to submit the data that was agreed upon in support of the electrode solution site transfer from — to Fair Lawn, New Jersey.

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(b). The safety update should include data from all non-clinical and clinical studies of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.
2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:
 - Present new safety data from the studies for the proposed indication using the same format as the original NDA submission.
 - Present tabulations of the new safety data combined with the original NDA data.
 - Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.
 - For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.

3. Present a retabulation of the reasons for premature study discontinuation by incorporating the dropouts from the newly completed studies. Describe any new trends or patterns identified.
4. Provide case report forms and narrative summaries for each patient who died during a clinical study or who did not complete a study because of an adverse event. In addition, provide narrative summaries for serious adverse events.
5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.
6. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.
7. Provide English translations of current approved foreign labeling not previously submitted.

In addition, submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to this division and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Within 10 days after the date of this letter, you are required to amend this application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. If you do not follow one of these options, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

Under 21 CFR 314.102(d), you may request an informal meeting or telephone conference with this Division to discuss what steps need to be taken before the application may be approved.

The drug product may not be legally marketed until you have been notified in writing that the application is approved.

If you have any questions, call Kimberly Compton, Regulatory Project Manager, at (301) 827-7432.

Sincerely,

{See appended electronic signature page}

Bob Rappaport, M.D.
Acting Director
Division of Anesthetic, Critical Care and
Addiction Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure

**This is a representation of an electronic record that was signed electronically and
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/s/

Bob Rappaport

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