QS#5688

UNITED STATES
CONSUMER PRODUCT SAFETY COMMISSION
WASHINGTON, DC 20207

VOTE SHEET

2001 MAY 10 P 12 13

Date MAY 7 2001

TO The Commission
Sadve E Dunn Secretary

FROM Michael S Solender General Counsel
Stephen Lemberg Assistant General Counsel
Patricia M Pollitzer Attorney

SUBJECT Petition PP 00 1 requesting a partial exemption for Lidoderm®

Ballot Vote Due MAY 17 2001

Attached is a briefing package from the staff concerning a petition from Endo Pharmaceuticals Inc (Endo) requesting that the Commission issue a partial exemption from special packaging requirements for its prescription drug Lidoderm® The petitioner asserts that special packaging is impracticable for Lidoderm® because of the high costs likely to place each Lidoderm® patch in child resistant packaging The staff recommends that the Commission deny the petition and instead grant a stay of enforcement with certain conditions A draft stay is attached to the briefing package at Tab B

Please indicate your vote on the following options

I The Petition

A Grant Petition PP 00 1 and direct the staff to prepare a draft notice of proposed rulemaking exempting Lidoderm from PPPA requirements

_________________________ _________________
Signature Date

B Deny Petition PP 00 1 and direct the staff to prepare a letter of denial to the petitioners

_________________________ _________________
Signature Date

6/4/01
5/16/01

CPSA 6 (b)(1) Cleared 5/7/01
WITH TAB A + 1
No Mfrs/PrvtLbrs or remove
Products Identified
Excepted by
Firms Notified
Comments Processed

C Defer decision on Petition PP 00 1

Signature _____ Date _____

D Take other action (please specify)

_____

_____

_____

Signature _____ Date _____

II The Draft Stay of Enforcement

A Approve the draft stay of enforcement

Signature _____ Date _____

B Approve the draft stay of enforcement with the following changes (please specify)

_____

_____

_____

Signature _____ Date _____

C Take other action (please specify)

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_____ _____

Signature Date

QS#5688

Briefing Package

Petition (PP 00 1) for a Partial Exemption for Lidoderm®
from the Special Packaging Requirements of the
Poison Prevention Packaging Act

For Information Contact
Jacqueline Ferrante Ph D
Directorate for Health Sciences
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5/14/01 P

CPSA 6 bi ii ear d 5/16/01 P

(6a) WITH FAB A ATS REMOVED

Products identified

Accepted Petition

Firms Notified

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Executive Summary

On August 14 2000 Endo Pharmaceuticals petitioned the Commission for a partial exemption for the orphan drug Lidoderm® from special packaging requirements The Food and Drug Administration designated Lidoderm® as an Orphan Drug on October 24 1995 and approved it for marketing on March 19 1999 In the U S orphan drugs are intended for rare diseases affecting less than 200 000 people or affecting more than 200 000 but for which there is no expectation that the costs of drug development will be recovered from sales To encourage the development of orphan drugs economic incentives such as tax credits and marketing exclusivity are included in the Orphan Drug Act

Lidoderm® is a lidocaine containing dermal patch used to treat post herpetic neuralgia (PHN) a rare painful condition that occurs predominantly in the elderly The Commission requires special or child resistant (CR) packaging under 16 C F R 1700 14 (a)(23) of the Poison Prevention Packaging Act (PPPA) for lidocaine products with more than 5 milligrams (mg) of lidocaine in a single package Each Lidoderm® patch contains 700 mg lidocaine Originally Lidoderm® was dispensed in a non CR carton containing six non CR resealable foil envelopes (each envelope contains five patches) for a total of 30 patches per carton

In May 1999 Commission staff discovered that Lidoderm® was packaged in non CR packaging and notified Endo of the special packaging requirement under the PPPA To comply with the PPPA the immediate container for the patch must be CR This can be achieved by either packaging each patch in an individual CR pouch or by using a single resealable CR pouch for all of the patches (i e no carton and no foil envelope only a resealable CR pouch) Endo responded that the PPPA requirement did not apply to lidocaine products in patch form and requested a stay of enforcement On May 15 2000 the Commission granted the stay on the condition that Endo 1) provide a CR pouch in the carton for pharmacists to put the foil envelopes in when dispensing Lidoderm® and 2) develop a plan to package each patch in a CR pouch

Given that Lidoderm® is an orphan drug Endo now argues that it would discontinue marketing Lidoderm if forced to place each patch in CR packaging because the current technology and set up at its manufacturing plant does not lend itself to this for both economical and practical reasons In its petition Endo proposes to use its interim solution (i e a single outer CR pouch containing six envelopes with five patches per envelope)

Based on available information the staff recommends that the Commission deny the petition because there are no reasonable grounds to exempt Lidoderm® from the special packaging requirements of the PPPA Instead the staff recommends that the Commission issue a stay of enforcement that allows Endo to use an outer CR package for Lidoderm® The stay should be predicated on several conditions including Lidoderm® remaining an orphan drug exclusively manufactured by Teikoku Seiyaku Co and Endo actively monitoring poisoning data for incidents involving Lidoderm®

OS#5688

United States
CONSUMER PRODUCT SAFETY COMMISSION
Washington D C 20207

MAY -7 2001

To	The Commission Sadye E Dunn Secretary
Through	Michael S Solender General Counsel MSl
Through	Pamela Gilbert Executive Director PG
From	Ronald Medford Assistant Executive Director Office of Hazard Identification and Reduction RM Jacqueline Ferrante Ph D Pharmacologist Directorate for Health Sciences JF
Subject	Petition (PP 00 1) for a partial exemption for Lidoderm® from the special packaging requirements of the Poison Prevention Packaging Act

I Background

Lidocaine a local anesthetic drug requires child resistant (CR) packaging under the Poison Prevention Packaging Act (PPPA) The Commission issued a CR packaging standard on April 10 1995 for all products with more than five milligrams of lidocaine in a single package with an effective date of one year Recognizing that more time may be needed to modify or replace certain package types (e g multiple dose tubes aerosols mechanical pumps etc) the Commission stated that affected parties using any type of package could apply for a temporary exemption for the minimum period required to market their products in CR packaging

In May 1999 Commission staff discovered that Endo Pharmaceuticals Inc made a prescription dermal patch with 700 mg of lidocaine per patch called Lidoderm® and packaged it in **non** CR packaging Lidoderm® is an orphan drug used to treat post herpetic neuralgia (PHN) The staff notified Endo of its obligation to package Lidoderm® in CR packaging on June 14 1999 In a letter dated June 29 1999 Endo responded that Lidoderm® was not subject to PPPA requirements because the standard does not apply to lidocaine products in patch form and the Commission does not have the statutory authority to enforce the standard against lidocaine patches (Tab A Section 8) Additionally attorneys for Endo claim that Commission staff (Dr Suzanne Barone PPPA project manager at the Commission)

advised them that the lidocaine standard did not apply to patches In that conversation Dr Barone responded to a general question about which products are covered by the PPPA with no specific reference to lidocaine She correctly informed Endo that the regulation for prescription drugs only covers oral dosage forms [16 C F R §1700 14(a)(10)]

However it is the Commission s position that the regulation for lidocaine applies to all products with more than 5 mg of lidocaine regardless of the formulation [1] Moreover the PPPA requires the immediate package (i e the package that is in direct contact with the product) to be CR After discussions with staff Endo proposed an interim voluntary compliance solution On May 15 2000 the Commission granted a stay of enforcement to allow Endo to use an outer CR package for Lidoderm® while it developed individual CR pouches for each patch Currently Endo is providing a reclosable CR pouch in the Lidoderm® carton with instructions for pharmacists to dispense the patches inside the pouch

On August 14 2000 Endo Pharmaceuticals Inc petitioned the Commission for a partial exemption for Lidoderm® from special packaging requirements stating that it is not practicable to market each Lidoderm® patch in a child resistant envelope (Tab B) The petitioner argues that to do so is cost prohibitive and would force them to discontinue production of Lidoderm® Endo is proposing to replace the carton with the CR pouch so that the six envelopes (5 patches per envelope) are marketed in the CR pouch not in the non CR carton

II Post Herpetic Neuralgia (PHN)

PHN is a rare chronic condition that results from nerve injury caused by shingles Shingles occurs following reactivation of the herpes zoster virus (the same virus responsible for chickenpox) and is characterized by painful fluid filled skin blisters Pain associated with PHN typically develops about a month after the rash and blisters associated with shingles heal PHN is more common in the elderly Approximately 10% of all patients with shingles develop PHN Endo estimates that about 200 000 Americans have PHN

The skin of PHN patients is so sensitive that a mild breeze or pressure from a bed sheet may cause pain Burning aching stabbing pain can last for months or years Many patients are unable to perform everyday activities because the pain is so severe There is no cure for PHN and treatment is aimed

[1]Lidocaine poisoning causes dose dependent cardiovascular and central nervous system effects including dizziness drowsiness convulsions coma and respiratory arrest The level for regulation of more than 5 mg is based on the recommended maximum single total dose of lidocaine in children (5 mg/kg or about 50 mg in a 10 kg child) divided by an uncertainty factor of 10 (50 mg divided by 10 = 5 mg)

at controlling the pain by various methods including drug therapy (e g analgesics antidepressants topical anesthetics and anticonvulsants) acupuncture and nerve block (Stankus et al Am Fam Physician 61 2437 44 2000)

III Product Information

Lidoderm® is a relatively new prescription product intended solely for the relief of pain associated with PHN Teikoku Seiyaku Co Ltd in Japan is the only company given approval to manufacture Lidoderm® by the U S Food and Drug Administration (FDA) The sole distributor of Lidoderm® in the U S is Endo Pharmaceuticals Inc The FDA designated Lidoderm® as an Orphan Drug on October 24 1995 under section 316 20 of the Food Drug and Cosmetic Act and approved it for marketing on March 19 1999 Endo started marketing Lidoderm® on September 15 1999

Orphan drugs are intended to be used for rare diseases or conditions which either 1) affect fewer than 200 000 people in the U S or 2) affect more than 200 000 in the U S but there is no reasonable expectation that the cost of developing and making the drug will be recovered from sales in the U S The Orphan Drug Act provides incentives to encourage interest in the development of orphan drugs including tax credits for clinical research and seven years of marketing exclusivity

Each carton of Lidoderm® contains 30 patches packaged in six resealable foil envelopes with five patches per envelope Neither the carton nor the individual envelopes are CR Currently Endo is including a CR reclosable pouch large enough for the six envelopes in each carton Each Lidoderm® patch is 22 square inches (10 cm x 14 cm) and contains 700 mg of lidocaine The amount of lidocaine systemically absorbed from Lidoderm® depends on both the duration of exposure and the surface area of skin coverage The recommended dose is up to three patches at one time only once for up to 12 hours in a 24 hour period Patches may be cut into smaller sizes prior to removal of the release liner Data related to the stability of the lidocaine in a cut or used patch were not provided but instructions on the product envelope advise that the patch adhesive contains water and will dry out if the package is left open

According to the petition Lidoderm® is unlike other patch systems in that the lidocaine in Lidoderm® is not contained in a reservoir but is embedded in the patch adhesive Therefore the patch releases a low level of lidocaine into the skin over a long time period ensuring that it produces analgesia (pain reduction) rather than anesthesia (numbness) Since only a small percentage (3% $\pm$ 2%) of lidocaine is absorbed dermally from the Lidoderm® patch when used therapeutically about 95% of the lidocaine will remain in a used patch However Endo reasons that the lidocaine is less accessible from their unique patch system than from other formulations (e g creams liquids etc) Additionally Endo states that a child would need to chew or suck on a portion of the patch for a certain amount of time before any lidocaine would

begin to be absorbed through the mucosa of the mouth or swallowed This implies that it would take a substantial amount of time to absorb a toxic dose following an oral exposure However there are no oral absorption data to support this claim Moreover product information provided by Endo warns patients that *Even a used patch contains a large amount of lidocaine (at least 665 mg) The potential exists for a small child or pet to suffer serious adverse effects from chewing or ingesting a new or used Lidoderm® patch although the risk with this formulation has not been evaluated Patients should store and dispose of Lidoderm® out of the reach of children and pets* This is important since oral exposures in children to drugs (e g nicotine) from patch formulations have been documented by the American Association of Poison Control Centers (AAPCC) (Woolf et al Pediatrics 99 (5) 724 1997) According to the petition the AAPCC informed Endo that as of August 9 2000 there were no reports of overdosing accidental exposure or poisoning by children with Lidoderm®

IV Discussion

According to the petitioner the justification for the partial exemption is that it is not practicable to market each Lidoderm® patch in a child resistant envelope As the petitioner acknowledges in a letter to the Commission dated June 29 1999 under the PPPA practicability means that special packaging complying with the standards can be produced using modern mass production and assembly line techniques In the final rule for lidocaine products the staff concluded and still maintains that special packaging for all lidocaine products is technically feasible practicable and appropriate (60 FR 17992) The rule contains no exemption for patches

The petitioner s argument actually addresses economic impracticality Endo does not argue that special packaging for Lidoderm® could not be mass produced but rather that it would be too expensive Endo maintains that the costs of new equipment plant re engineering and testing for FDA approval are prohibitive and would force them to discontinue marketing Lidoderm® (Section V of the petition) Teikoku estimates a total cost of abo[redacted]r the changes required to place each patch in a CR pouch This includes the cost of 1) four new envelope processing machines 2) producing three FDA submission batches 3) extended specification compliance testing on all three batches 4) accelerated stability testing and 5) real time stability testing The petitioner maintains that manufacturing and packaging one patch per envelope would result in a[redacted]n the cost of manufacturing Lidoderm® because there would be significant increases in the amount of labor and materials

Additionally Endo argues that it would tak[redacted]imes longer than the current packaging method to produce an equivalent amount of Lidoderm® in individual CR pouches Endo reasons that this change in the production schedule for Lidoderm®

is an undue burden for Teikoku because it affects the production of other products Teikoku is unwilling to allow another manufacturer to take over production because the manufacturing process for Lidoderm® is proprietary

Another packaging option for the petitioner that meets PPPA requirements is to place all of the patches in a large CR pouch so that the immediate package is the pouch not the non CR envelopes This approach would require stability testing and possibly the development of a new CR package if existing packaging did not prove suitable for Lidoderm® Endo did not provide cost estimates for this option

Given the information in the petition the staff cannot verify the accuracy of the estimated costs However regardless of whether the staff agrees with the cost estimates Endo maintains that it will discontinue production of Lidoderm® if forced to place each patch in CR packaging As a result Lidoderm® would no longer be a therapeutic option for PHN patients

The petitioner is not requesting a complete exemption from the special packaging requirements for lidocaine Specifically Endo is asking to replace the outer carton for Lidoderm® with a CR reclosable pouch containing six resealable foil envelopes (5 patches per envelope) rather than placing the patches in immediate CR packaging as required by the PPPA [redacted]

The PPPA provides for exemptions but the petitioner must provide justification based on one or more of the following grounds the lack of toxicity of the substance evidence that special packaging is not technically feasible practicable and appropriate or that the special packaging is incompatible with the substance None of these conditions applies to Lidoderm® The toxicity of lidocaine is unequivocal and the required special packaging is technically feasible practicable and appropriate

However because Lidoderm® is an orphan drug that Endo states it will discontinue if required to use CR packaging for individual patches the Commission could issue a stay of enforcement so that Lidoderm® can remain available to PHN patients The stay could be issued with conditions The staff suggests the following conditions

1) Lidoderm® must be marketed in the proposed outer CR package
2) Endo Pharmaceuticals must label the CR pouches warning of the toxicity of lidocaine and the importance of storing unused patches inside the CR pouch to protect children from accidental exposure

3) Lidoderm® must remain an orphan drug for the treatment of PHN to limit its availability
4) Lidoderm® must be manufactured only at Teikoku Seiyaku Co Ltd in Japan under the operating conditions described in the petition Endo Pharmaceuticals must notify the Commission immediately if it plans to manufacture Lidoderm® at a different location
5) Endo Pharmaceuticals must monitor poisoning data and immediately notify the Commission of any incidents

V Options

A Grant the petition

The Commission may grant the petition and issue a proposed exemption if it concludes that 1) providing a partial exemption for Lidoderm® does not present a risk of serious personal injury or illness to young children or 2) special packaging is not technically feasible practicable and appropriate

B Deny the petition

The Commission may deny the petition if it concludes that the petitioner has not provided justification for an exemption

C Defer the petition

The Commission may defer the petition if it concludes that more information is needed to decide whether to grant or deny the petition

D Deny the petition and issue a conditional stay of enforcement

The Commission may deny the petition and issue a stay of enforcement for Lidoderm® patches with conditions such as the following

1 Lidoderm® must be marketed in CR packaging as outlined in Section IV of the petition

2 Endo Pharmaceuticals must provide a warning label on the outer CR package concerning lidocaine toxicity and the importance of keeping unused patches inside the CR package to protect children from accidental exposure

3 Lidoderm® must remain an orphan drug for the treatment of PHN

4 Lidoderm® must be manufactured only at Teikoku Seiyaku Co Ltd in Japan under the operating conditions described in the petition Endo Pharmaceuticals must notify the Commission immediately if it plans to manufacture Lidoderm® at a different location

5 Endo Pharmaceuticals must monitor poisoning data for exposures involving Lidoderm® and immediately notify the Commission of any incidents reported directly to them or indirectly through a poison control center doctor or emergency room

VI Conclusion and Recommendation

Lidoderm® is an orphan drug approved by the FDA for pain relief from PHN a debilitating condition common in the elderly Endo Pharmaceuticals is the only distributor of Lidoderm® in the U S According to Endo there are no reports of accidental exposure to Lidoderm® involving children since marketing in non CR packaging began in September 1999

Endo claims that it will discontinue marketing Lidoderm® if the Commission requires CR packaging for each patch because of the excessive cost This may adversely impact PHN patients who benefit from using Lidoderm® Endo is currently providing an outer CR pouch in each carton of Lidoderm® with instructions for pharmacists to remove the six envelopes of patches from the carton and dispense them to patients in the CR pouch Rather than provide immediate or primary packaging Endo is requesting that the Commission allow them to replace the outer non CR carton for Lidoderm® with a CR pouch that will hold six envelopes of five patches per envelope (total = 30 patches per CR pouch)

While there is no legal justification for an exemption denying the petition and issuing a stay of enforcement for Lidoderm® with conditions would offer a balance between protecting young children from potential harm and giving PHN patients continued access to the drug The staff recommends that the Commission deny the petition and issue a stay of enforcement allowing Endo to use outer CR packaging for Lidoderm® but only under the conditions outlined above (Section V part D)

If the Commission grants the stay Endo must file an annual report confirming that the conditions of the stay remain in effect Additionally Endo must notify the Office of Compliance 30 days in advance of any change that may affect its compliance with any provision of the stay The Commission may revoke the stay at any time if new information shows that the outer CR packaging does not adequately protect children from serious harm or if any of the conditions are violated

TAB A

PP-00-1

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August 14 2000

MFR/PRVLBR NOTIFIED 2/13/01
No Comments made
Comments attached
Excisions/Revisions
Firm has not requested
further notice

Office of the Secretary
Consumer Product Safety Commission
4330 East West Highway
Room 502
Bethesda, Maryland 20814

PETITION FOR PARTIAL EXEMPTION FROM SPECIAL PACKAGING REQUIREMENT

Pursuant to Part 1702 of the Commission s regulations at 16 C F R , and on behalf of Endo Pharmaceuticals, Inc (Endo) Chadds Ford Pennsylvania, the undersigned file this petition for a partial exemption from the special packaging requirements the Commission seeks to enforce against Endo's prescription drug product Lidoderm® (lidocaine patch 5%) The justification for the partial exemption is that it is not practicable to market each Lidoderm® patch in a child resistant envelope as the Commission staff have requested

I LIDODERM®

A Product and Packaging Description

Lidoderm® is comprised of an adhesive material attached to a [redacted] film release liner The release liner is removed prior to applying the adhesive side of the patch to the area of the body to be treated

Lidoderm® is a unique patch The active ingredient, 700 mg of lidocaine (50 mg per gram of adhesive), is uniformly blended with the adhesive on the patch This means that, unlike other patch drug products, Lidoderm® does not have a reservoir of active drug substance Therefore, manipulation or cutting of the patch will not affect the release profile of lidocaine This proprietary system is unique in the United States and no other legend pharmaceutical patch is produced in this manner Other patches may have reservoirs or matrixes that contain the active ingredient These systems may release all of the active ingredient if damaged

When Lidoderm® is applied directly over the affected area, low doses of lidocaine diffuse slowly from the adhesive layer and into the epidermal and dermal layers of the skin Three Lidoderm® patches will give a peak plasma level of 0 13 µg/mL A blood level over 3 µg/mL is required for analgesia The suggested mechanism of action of Lidoderm® is the blockage of sodium channels in damaged nerve fibers Lidoderm® will cause a reduction of pain (analgesia) without significant numbness (anesthesia) This is in direct contrast to the EMLA® lidocaine patch and topical lidocaine products which, if used for postherpetic neuralgia, would cause anesthesia, not analgesia

The Lidoderm® patch is a 22 square inch patch (10 cm x 14 cm) This is substantially larger than most patches in the U S market For comparison, the Catapres® (clonidine) patch is 0 6 square inches, the Nicoderm® (nicotine) patch is 1 6 square inches, the Duragesic® (fentanyl) patch is 3 4 square inches, and the EMLA® (lidocaine) patch is 6 25 square inches Lidoderm® also differs in that it is very pliable so as to conform to the contours of the part of the body to which it is applied

Lidoderm® is supplied in the form of five patches inside a resealable foil envelope The foil envelope must be resealable to maintain the integrity of the product, as no more than three patches are recommended for use within a 24 hour period and there are five patches in each envelope Six envelopes are contained in one carton The specifications for the patch the envelope and the box are included as Attachment 1 One sample of the product as packaged (i e carton with six envelopes inside) is included as Attachment 2

Lidoderm® is manufactured in Japan by Teikoku Seiyaku, Co , Ltd ("Teikoku') Teikoku is the only manufacturer approved by the Food and Drug Administration (FDA) anywhere in the world to manufacture and supply Lidoderm® for the U S market Endo is the exclusive distributor of Lidoderm® in the U S Teikoku and the U S developer Hind

Healthcare, Inc , are the owners of the approved NDA (new drug application) and the patent for the development of the product

B Marketing History

On October 24 1995, FDA designated Lidoderm® as an 'orphan drug" for the relief of allodynia (painful hypersensitivity) and chronic pain in post herpetic neuralgia (see Attachment 3) An orphan drug is a drug intended to treat a rare condition that affects fewer than 200,000 persons in the U S , or affects more than 200,000 persons but for which there is no reasonable expectation that the cost of developing and making available the drug will be recovered from sales [1] The orphan drug provisions of the Federal Food, Drug and Cosmetic Act (FDC Act) are intended to encourage the development and marketing of drugs for rare diseases through the use of certain economic incentives [2] Without these economic incentives, the rare condition would go untreated with drugs Attachment 4 explains in more detail the nature of orphan drugs

FDA approved Lidoderm® for marketing for the relief of pain associated with post herpetic neuralgia on March 19 1999 (see Attachment 5) The FDA approved package insert for Lidoderm® is Attachment 6 Endo began marketing Lidoderm® on September 15 1999 and 123 572 cartons have been distributed since then

The dispensing statistics available to Endo at this time show that the average prescription size for Lidoderm® since launch of the product is 28 7 patches, which equals almost six (5 74) envelopes (one carton) For the first quarter of this year the average prescription size increased to 29 1 patches, which also equals about six (5 82) envelopes

C Patient Need for Lidoderm®

Lidoderm® is the only drug that FDA has approved for the relief of pain associated with postherpetic neuralgia Postherpetic neuralgia is a neuropathic pain syndrome that is

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1 21 U S C § 360bb(a)(2)

2 See e g 21 U S C § 360cc

most commonly defined as pain persisting or recurring in the region of herpes zoster (shingles) eruption at least one month after the rash has healed [3]

Postherpetic neuralgia is characterized by three types of pain (1) a constant, deep, aching or burning pain (2) an intermittent pain with a sharp, lancinating or jabbing quality, and (3) a dysesthetic pain provoked by normally innocuous stimuli such as light touch, heat, or cold (allodynia), that lasts well beyond the duration of the stimulus (hyperpathia) Paradoxically in addition to this painful hypersensitivity patients with postherpetic neuralgia may develop concomitant sensory deficit, experiencing, for example, a sensation of numbness within the painful area These sensory abnormalities may extend well beyond the boundary of the initial herpes zoster eruption [4]

The risk of developing postherpetic neuralgia increases with age and the elderly are at a greatly increased risk Approximately 27% of patients over age 55, 47% of patients over age 60 and 73% of patients over age 70 develop postherpetic neuralgia after having shingles [5] Thus the vast majority of patients who use Lidoderm® are the elderly

Because the pain of postherpetic neuralgia may become intractable over a period of months to years postherpetic neuralgia can prevent patients from carrying on normal daily activities such as dressing bathing, grooming (due to tactile allodynia), traveling shopping and cooking Tactile allodynia may result in such unbearable pain that patients are unable to wear clothing on the affected body part, potentially restricting their ability to venture outside the home and contributing to their social isolation The cumulative effect of these factors is a significant reduction in the patients quality of life and increased use of healthcare resources [6]

Because of the complex etiology of postherpetic neuralgia, its treatment has typically involved the empirical use of traditional analgesic and anesthetic drugs opioids,

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[3] Irving GA, Wallace MS Herpes zoster and postherpetic neuralgia In *Pain Management for the Practicing Physician* Philadelphia, PA Churchill Livingstone 1997 141 147

[4] Choo PW Galil K, Donahue JG Walker AM Spiegelman D Platt R Risk factors for postherpetic neuralgia *Arch Intern Med* 1997 157 1217 1224

[5] Kost RG Straus SE Postherpetic neuralgia pathogenesis treatment and prevention *N Engl J Med.* 1996 335 32-42

[6] Schmader K Postherpetic neuralgia in immunocompetent elderly people *Vaccine* 1998 16 1768 1770

capsaicin and neuroactive agents such as tricyclic antidepressants and antiepileptic drugs Variable success has also been reported with transcutaneous electrical nerve stimulation (TENS), nerve blocks and, as a last resort, surgery [7] However, none of these medications or therapeutic modalities have been approved by FDA for the treatment of postherpetic neuralgia

Lidoderm® is the first and only treatment approved by FDA specifically for the relief of pain associated with postherpetic neuralgia With its unique delivery system, and when applied directly to intact skin, Lidoderm® penetrates the skin, soft tissues and peripheral nerves without producing clinically significant serum drug levels and with little risk of systemic side effects or complete anesthetic block

With few side effects Lidoderm® can fill some of the tremendous need for pain relief that exists in this patient population As confirmation of this unmet medical need Attachment 7 consists of several histories of sufferers of postherpetic neuralgia who participated in the clinical trials for Lidoderm® and whose pain was significantly relieved by Lidoderm®, as well as some testimonials of new patients since launch

D How Lidoderm® is Used

Upon reactivation, the virus that causes shingles will spread along a nerve to the skin erupting in multiple places along the skin following the entire nerve This broad distribution of pain may require up to three patches to cover as much of the painful areas as possible

The recommended dosage is up to three patches, once for up to 12 hours within a 24 hour period Typical parts of the body where Lidoderm® is applied are as follows torso >50%, face/eye area, 20%, lower back and neck 20% In addition as seen in the following figure, significant portions of patients have pain for longer than one year [8]

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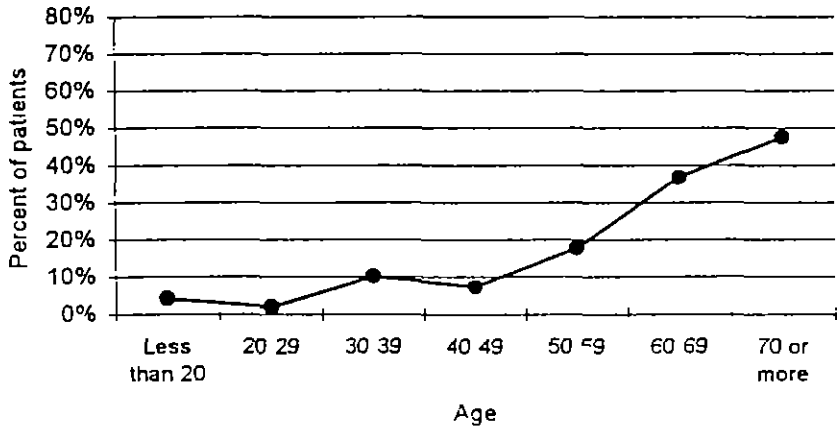
[7] Gershon AA Epidemiology and management of postherpetic neuralgia *Semin Dermatol* 1996 15 (suppl 1) 8 13

[8] De Moragas JM Kierland RR, The outcome of patients with herpes zoster Archives of Dermatology 1957 75 193 6

Figure 2 Patients with Post Herpetic Neuralgia lasting over 1 year



II REGULATION AT ISSUE

On April 10 1995, four years before Lidoderm® was approved for marketing, the Commission published a final rule (effective April 10, 1996) providing that products containing more than 5 0 mg of lidocaine in a single package (i e retail unit) shall be packaged ' in child resistant packaging [9]

In December of 1998 Endo asked this law firm to investigate the applicability of the standard to lidocaine patches A review of the notice of proposed rulemaking,[10] the 1992 Briefing Package of the Commission's Directorate for Health Sciences, and the final rule, revealed that the Commission made the findings required by the Poison Prevention

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9 60 Fed Reg 17992 codified at 16 C F R § 1700 14(a)(2ɔ)

10 57 Fed Reg 34274 (Aug 4, 1992)

Packaging Act (PPPA) only with respect to (1) the following dosage forms creams ointments, gels, jellies, viscous solutions liquids sprays, aerosols, and injectables and (2) the following types of packaging tube packaging squeeze or pump bottles and 'aerosol sprays [11] The Commission considered also prefilled syringes and a product in a foil packet containing 1/8 oz of gel '[12]

Because the findings required by the PPPA were not made with respect to lidocaine patches and based on well settled principles of administrative law we concluded that the regulation could not be construed to apply to lidocaine patches, either reasonably or legally In addition, on December 10, 1998, a representative of this law firm discussed the applicability of the regulation with a member of the Commission's staff who was identified as the contact person for the child resistant packaging regulations We were informed that the standard for lidocaine products was not intended to apply to lidocaine patches because they were not on the market at the time the standard was proposed and finalized The staffer added that the Commission was 'in the process of formulating its policy on patch products [13]

Thus even after consulting with Commission staff Endo had no reason to believe that the standard would apply to lidocaine patches However in a June 14 1999 letter to Endo the Commission staff stated that Lidoderm® was required to comply with the standard

III INAPPLICABILITY OF REGULATION TO LIDOCAINE PATCHES

In previous correspondence Endo has explained the bases for its position that the standard legally cannot be interpreted to apply to lidocaine patches, that the Commission does not have statutory authority to enforce the standard against lidocaine patches and that Endo s Lidoderm® therefore is not misbranded under section 502(p) of the FDC Act Endo's arguments in this regard are set forth in its letters of June 29 1999 and September 7 1999 which are included as Attachments 8 and 9 to this petition and incorporated by reference

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[11] See e g 60 Fed Reg at 17993 94, 18002 03

[12] Id at 17994 18001

[13] The Commission staff have indicated that we misunderstood the statements that were made

IV ENDO'S VOLUNTARY COMPLIANCE

Despite the inapplicability of the regulation to Lidoderm®, Endo has been working with the staff at trying to find a mutually satisfactory resolution As the first step, and without admitting the applicability of the regulation to Lidoderm® Endo petitioned for a stay of enforcement, which stay was granted by letter of June 2, 2000

As an interim (short term) voluntary compliance measure Endo has obtained child resistant recloseable pouches A sample of this pouch is enclosed as Attachment 10 Effective August 1 2000, each carton of Lidoderm® shipped to customers contains one of these child resistant pouches Endo has sent a letter to pharmacists (Attachment 11) informing them of the availability of the pouches, and instructing them to dispense Lidoderm® only in the child resistant pouches Each child resistant pouch can hold six Lidoderm® envelopes which is the current average prescription size In addition a statement was added to the Lidoderm® carton and the child resistant pouch to emphasize that the product must be dispensed in the child resistant pouch (see Attachments 10 and 12)

In exploring a permanent voluntary compliance measure, Endo considered packaging the five patches in a resealable, child resistant envelope However no such packaging is currently available As explained in section V of this petition it is not practicable to package each Lidoderm® patch in a child resistant envelope Thus as the permanent voluntary compliance measure Endo has determined that the only viable alternative is to replace the current carton with the child resistant pouch that is now being included inside the carton The child resistant pouch would be labeled with the same information that now appears on the carton

A detailed timeline has been developed for implementing this permanent solution (see Attachment 13) This permanent solution can be implemented, and product in a child resistant pouch can be available to customers, by May 31, 2001 This would eliminate the need for the pharmacist to place the product in a child resistant container as all Lidoderm® would be supplied in a child resistant pouch containing 30 patches (six envelopes) The labeling would also be revised to instruct patients to always store the envelopes inside the child resistant pouch

For this permanent solution, Teikoku, the manufacturer, will need to purchase a heat sealing machine at a cost of [redacted] The heat sealing machine is

necessary to seal the child resistant pouch once the envelopes are placed inside it The child resistant pouch will be supplied to Teikoku with the zipper in the closed and locked position with the top of the pouch left open Teikoku will place six envelopes into the child resistant pouch through the open top and then pass the top of the child resistant pouch through the heat sealing machine to seal it closed

The cost to manufacture and package six envelopes (each containing five patches) into the child resistant pouch is estimated to be [redacted] increase over the current cost of goods, due to the additional labor and material cost Additional labor is necessary because the current method for packaging the envelopes into a carton is not the same method used to place the envelopes into the child resistant pouch method

Currently, as the envelopes come off the packaging/sealing line they move on a convevor belt where they are manually placed directly into the carton the carton is sealed, and placed into shippers (cardboard box containing sixteen cartons) To package the envelopes into the child resistant pouch, the envelopes must be first transported to a different room which houses the heat sealing machine, because there is no space for the heat sealing machine in the room currently used to package the envelopes into cartons The child resistant pouches then must be manually and individuallv opened and formed so that the six envelopes will fit inside Once the six envelopes are placed inside, the top of the child resistant pouch must be heat sealed and placed into a shipper Teikoku estimates that this procedure is more labor intensive, will take longer and therefore will be more expensive to complete In addition, the cost of the child resistant pouch is estimated to be [redacted] whereas that of the carton is on[redacted]

Additional burdens to making these changes to the packaging process would be the required notifications to FDA relating to the changes in the secondary packaging and the use of an additional room for heat sealing the pouches

Nevertheless, Endo and Teikoku are willing to undertake this massive endeavor to cooperate with the Commission because the alternative proposed bv the Commission staff will destroy the marketability of the product.

V NEED FOR RELIEF

The Commission staff have informed Endo that each patch of Lidoderm® must be in a child resistant envelope This is apparently based on the definition of package in the

PPPA, which refers to the "immediate" container [14] Endo has determined that the costs involved in this approach will be prohibitive

Teikoku has assessed the feasibility of packaging each Lidoderm® patch in a child resistant envelope and informed Endo that its current equipment cannot accommodate the thicker child resistant material that is used for packaging the EMLA® patch [15] The EMLA® material is thicker and less pliable than the material used to make the Lidoderm® envelope Teikoku h[redacted]machines that have been validated to package Lidoderm® in the current envelopes If Teikoku were to package each Lidoderm® patch in a child resistant envelope, Teikoku would need to purcha[redacted]ew envelope processing machines capable of handling the child resistant material Teikoku estimates that the capital cost alone for these new machines would be[redacted]per machine)

Teikoku would also incur the costs for re engineering the plant to accommodate the new equipment, performing installation qualification performance qualification and operational qualification, repeating stability studies in the new material and submitting these data for prior approval to the FDA These additional costs are estimated a[redacted] The total estimated cost would be[redacted]broken down as follows

Activity	Cost
Purcha[redacted]ew machines	[redacted]
Manufacture three FDA submission batches	[redacted]
Extended specification compliance testing on all three batches	[redacted]
Accelerated stability testing	[redacted]
Real time stability testing	[redacted]
+/ 10%	
Total	[redacted]

Manufacturing and packaging one patch per envelope would result in an increase of [redacted]n the cost of manufacturing Lidoderm® because there would be significant increases

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[14] 15 U S C § 1471(3)

[15] The Commission staff have informed Endo that the EMLA® patch is contained in a child resistant foil packet

in the amount of labor and materials (five envelopes with one patch each versus the current one envelope with five patches) Teikoku estimated that the labor would increase fro[redacted] days t[redacted] production to manufacture and package an equivalent amount of patches If this approach for packaging Lidoderm® were to be taken Endo would incur a negative [redacted] profit margin at the current price of Lidoderm®

Currently, Teikoku has the capacity to manufactu[redacted] patches and package [redacted] lopes in one day The process for manufacturin[redacted] patches includes manufacturi[redacted] atche[redacted] f lidocaine paste' and applying it to the patch material i[redacted] The process includes [redacted] efore the patches are put into the envelopes The patches must be packaged in the envelopes with[redacted] urs of being manufactured After the Lidoderm® patches ha[redacted] stacks of five each stack of five patches is placed into an envelope and sealed

If Teikoku were to manufacture and package one patch per envelope, o[redacted] patches could be made in one day because of the limitation in the capacity to package [redacted] nvelopes per day Thus it would ta[redacted] long to produce an equivalent of product under the one patch to one envelope scena[redacted]

Teikoku alloc[redacted] vs a month for the production of Lidoderm® Thus if each patch must be packaged in its own envelope, an addition[redacted] ould be needed to produce the same amount of Lidoderm® currently produced These addit[redacted] not available because other Teikoku customers use the remainder of their production time each month It would be an undue burden for Teikoku to accommodate this kind of change in their production schedule or take time from other customers' production needs In addition Teikoku the only FDA approved manufacturing site for Lidoderm® [16] is not willing to transfer this manufacturing technology to another manufacturer since the manufacturing process is proprietary technology belonging solely to Teikoku

The above discussion does not even take into consideration that existing child resistant envelopes might not prove suitable for Lidoderm® as no testing has been done to make this determination Due to the uniqueness of the Lidoderm® technology what might be suitable for other lidocaine patches or for other patch products in general might

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[16] Under the FDC Act a new drug may be manufactured only in a facility and using a process that FDA has approved as part of the new drug application for the product

nevertheless fail to adequately protect the integrity of Lidoderm® or might interfere with its intended storage or use [17]

In summary, the current technology and set up at Teikoku's manufacturing plant does not lend itself to the immediate package being child resistant for both economical and practical reasons If Endo were forced to package each patch in a child resistant envelope Endo could not continue marketing Lidoderm® and this orphan drug would no longer be available to patients in the United States

Therefore the only permanent solution that would allow Endo to continue marketing the product is to manufacture and sell Lidoderm® in a child resistant pouch containing six envelopes each envelope containing five patches

VI NO CHILDREN POISONINGS WITH LIDODERM®

Neither Endo nor Teikoku has ever received a report of a child being prescribed Lidoderm® No adverse events or accidental exposures attributed to children have ever been reported The world literature is bereft of any reports of Lidoderm® poisoning The American Association of Poison Control Centers informed Endo that, as of August 9 2000, there were no reports of overdosing accidental exposure, or poisoning by children with Lidoderm®

As stated above, application of three Lidoderm® patches to the skin for 12 hours results in a peak plasma level of 0 13 µg/mL This is about 20 times less than the amount at which lidocaine begins to have any systemic effects (2 5 µg/mL) [18] It should be noted that the lowest blood level of lidocaine mentioned in the Commission s 1992 Briefing Package as having an adverse effect on a child was 4 5 µg/ml, measured six hours after oral

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[17] One of the findings that the PPPA requires the Commission to make in order to impose a special packaging requirement is that the special packaging be appropriate ' 60 Fed Reg at 8002 Appropriateness exists when packaging complying with the standard will adequately protect the integrity of the substance and not interfere with the intended storage or use *Id*

[18] 1992 Briefing Package for lidocaine products at 56

administration of a liquid preparation to a five month old child [19] Thus skin contact with Lidoderm® should not present a risk of serious injury or illness to a child [20]

In addition, unlike other dosage forms of lidocaine (creams ointments, jellies, liquids sprays, which were the dosage forms evaluated by the Commission in the rulemaking for lidocaine products), access to lidocaine from Lidoderm® is not easily had A child would need to chew or suck on a portion of the patch (which is too big to be placed entirely in the mouth) for a certain amount of time before any lidocaine would begin to be absorbed through the mucosa of the mouth or swallowed As explained above, there is no readily available reservoir ' of lidocaine in Lidoderm®—the lidocaine is embedded in and part of the adhesive to control its release from the patch Thus Lidoderm® does not present the same degree of poisoning risk to children as other lidocaine products

VII THE COMMISSION HAS AUTHORITY TO GRANT THIS PARTIAL EXEMPTION

Both the Commission s regulations[21] and the legislative history of the PPPA[22] provide that the Commission has broad discretion to exempt categories of substances subject to special packaging requirements ' and "provide such exemptions while prescribing such special packaging requirements ' or by subsequently amending the prescribing regulation The Commission also has power to determine specifically the parameters of special packaging ' [23]

VIII CONCLUSION

The PPPA instructs the Commission to take into consideration the technical feasibility practicability and appropriateness of a special packaging standard [24] Endo's situation as explained in this petition perfectly illustrates the importance of these considerations Congress did not intend to authorize the Commission to destroy the

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19 *Id* at 57 (the child recovered fully within 24 hours)

20 For purposes of this discussion, Endo is assuming that the PPPA was intended to prevent this type of poisoning (non ingestion) although this is not clear

21 16 C F R § 1702 1

22 H Rep No 91 1755 at 9 (1970)

23 S Rep No 91 845 at 9 (1970)

24 15 U S C § 1472(a)(1)

viability of a product or to take a position that has the practical result of banning" a product, particularly one intended to ease human suffering

Based on the above, Endo Pharmaceutical respectfully petitions the Commission to authorize Endo to comply with the special packaging standard at 16 C F R. § 1700 14(a)(23) by using a child resistant outer container

Respectfully submitted,

HYMAN, PHELPS & MCNAMARA, P C
Counsel for Endo Pharmaceuticals Inc

By Samia N Rodriguez

SNR/drc

ATTACHMENTS

TABLE OF CONTENTS

FRONT OF BOX

ENDO LABORATORIES
Endo® LIDODERM®
(lidocaine patch 5%)

LOT:
EXP:

N 3 63481 687 06 2

NDC 63481-687-06

ENDO LABORATORIES
Endo® LIDODERM®
(lidocaine patch 5%)

Each adhesive patch contains:
Lidocaine..... 700 mg (50 mg per gram adhesive)
in an aqueous base. Methylparaben and propylparaben as preservatives.

DOSAGE: For dosage and full prescribing information, read accompanying product information.

Store at 25°C (77°F); excursions permitted to 15°-30°C (59°-86°F).

WARNING: Package not child resistant. Keep used and unused patches out of the reach of children and pets.

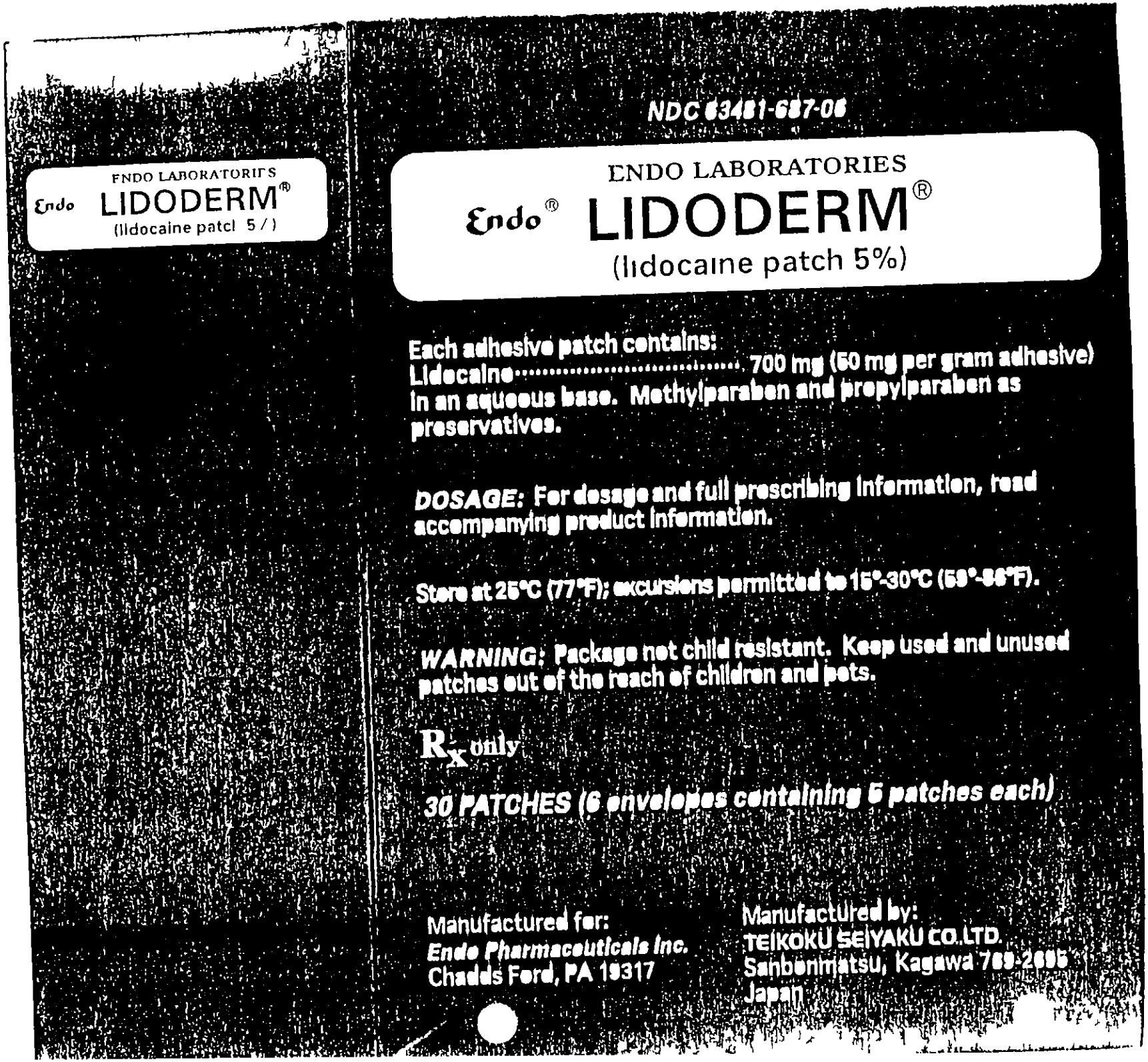
R_x only

30 PATCHES (6 envelopes containing 5 patches each)

Manufactured for:
Endo Pharmaceuticals Inc.
Chadds Ford, PA 19317

Manufactured by:
TEIKOKU SEIYAKU CO.,LTD.
Sanbonmatsu, Kagawa 769-2695
Japan

BACK OF BOX


ENDO LABORATORIES
Endo LIDODERM®
(lidocaine patch 5%)
NDC 63481-687-06
ENDO LABORATORIES
Endo® LIDODERM®
(lidocaine patch 5%)
Each adhesive patch contains:
Lidocaine..... 700 mg (50 mg per gram adhesive)
in an aqueous base. Methylparaben and propylparaben as
preservatives.
DOSAGE: For dosage and full prescribing information, read
accompanying product information.
Store at 25°C (77°F); excursions permitted to 15°-30°C (59°-86°F).
WARNING: Package not child resistant. Keep used and unused
patches out of the reach of children and pets.
Rx only
30 PATCHES (6 envelopes containing 5 patches each)
Manufactured for:
Endo Pharmaceuticals Inc.
Chadds Ford, PA 19317
Manufactured by:
TEIKOKU SEIYAKU CO.LTD.
Sanbonmatsu, Kagawa 769-2695
Japan

FRONT OF ENVELOPE

Cut along dotted line and pull open seal

IMPORTANT
Reseal after opening

NDC 63481-687-05

ENDO LABORATORIES

Endo® LIDODERM®

(lidocaine patch 5%)

Each adhesive patch contains:
Lidocaine .....700 mg (50 mg per gram adhesive) in an aqueous base. Methylparaben and propylparaben as preservatives.

DOSAGE: For dosage and full prescribing information, read accompanying product information.

Store at 25°C (77°F); excursions permitted to 15°-30°C (59°-86°F).

WARNING: Package not child resistant. Keep used and unused patches out of the reach of children and pets.

R_x only

5 PATCHES (10 CM X 14 CM EACH)

Manufactured for:
Endo Pharmaceuticals Inc.
Chadds Ford, PA 19317

Manufactured by:
TEIKOKU SEIYAKU CO.,LTD.
Sanbonmatsu, Kagawa 769-2695
Japan

BACK OF ENVELOPE

DIRECTIONS FOR USE

Cut the outer seal from the package along the dotted line and pull apart the zipper seal.

Remove the desired number of patches and reseal the package using pressure on the zipper seal. The adhesive contains water and will dry out if the package is open.

Remove the transparent release liner before application of patches to the skin.

Apply up to three (3) LIDODERM® patches at one time to cover the most painful area. Apply patches only once for up to 12 hours in a 24-hour period. Remove patches if irritation occurs.

N 3 63481 687 05 5

9437/0B

LOT: 6916

EXP: 2002 05

LIST OF ORPHAN PRODUCTS DESIGNATIONS AND APPROVALS

Through December 31 1998

NAME Generic Name TN=Trade Name	INDICATION DESIGNATED	SPONSOR & ADDRESS DD=Date Designated MA=Marketing Approval
Levocarnitine TN= Carnitor	Treatment of zidovudine-induced mitochondrial myopathy	Sigma-Tau Pharmaceuticals, Inc. 800 S Frederick Avenue, Suite 300 Gaithersburg MD 20877 DD=04/07/1997 MA / /
Levomethadyl acetate hydrochloride TN Orlaam	Treatment of heroin addicts suitable for maintenance on opiate agonists	Biodevelopment Corporation 8180 Greensboro Drive Suite 1000 McLean, VA 22102 DD=01/24/1984 MA=07/09/1993
Lidocaine patch 5 / TN= Lidoderm Patch	For relief of allodynia (painful hypersensitivity) and chronic pain in post-herpetic neuralgia.	Hind Health Care, Inc. 3707 Williams Rd. Suite 101 San Jose, CA 95117 DD=10/24/1995 MA= / /
Liothyronine sodium injection TN Triostat	Treatment of myxedema coma/precoma.	SmithKline Beecham Pharmaceuticals One Franklin Plaza P O Box 7929 Philadelphia, PA 19101 DD=07/30/1990 MA 12/31/1991
Lipid/DNA human cystic fibrosis gene TN	Treatment of cystic fibrosis	Genzyme Corporation P O Box 9322 One Mountain Road Framingham, MA 01701 DD=04/08/1996 MA / /
Liposomal Cyclosporin A TN= Cyclospire	For aerosolized administration in the prevention and treatment of lung allograft rejection and pulmonary rejection events associated with bone marrow transplantation.	Vernon Knight, M D Baylor College of Medicine Dept. of Molecular Physiology One Baylor Plaza Houston, TX 77030 DD=04/30/1998 MA= / /
Liposomal N Acetylglucosminyl N Acetyl muramly L-Ala D-isoGln L-Al a -glycerolidpalmitoyl TN= ImmTher	Treatment of osteosarcoma.	Endorex Corp 900 North Shore Drive Lake Bluff, IL 60044 DD=06/10/1998 MA= / /
Liposomal N Acetylglucosminyl N Acetyl muramly L-Ala D-isoGln L-Al a -glycerolidpalmitoyl TN= ImmTher	Treatment of Ewing s sarcoma.	Endorex Corp 900 North Shore Drive Lake Bluff, IL 60044 DD=06/10/1998 MA= / /
Liposomal amphotericin B TN= AmBisome	Treatment of cryptococcal meningitis	Fujisawa USA, Inc. 3 Parkway North Center Deerfield, IL 60015 DD=12/10/1996 MA=08/11/1997

APPROVED DRUG PRODUCTS WITH THERAPEUTIC EQUIVALENCE EVALUATIONS

U.S. Food and Drug Administration

OOPD Program Overview

Purpose of the Orphan Products Program

The Office of Orphan Products Development (OOPD) located in the Office of the Commissioner Food and Drug Administration (FDA) administers the orphan products development program This program is essentially involved in the identification of orphan products and the facilitation of their development Although the OOPD Grants Program has been expanded to include clinical studies for medical foods and devices that meet the ' orphan" criteria established by Congress the Orphan Drug Act pertains primarily to drug and biological products

This introduction will provide a general overview of the organization and operation of the orphan products program at FDA For further guidance and direction, additional and more specific information is available on the topics covered here

Congressional Action

The Orphan Drug Act (P L 97-414) amended the Federal Food Drug and Cosmetic Act (FFDCA) as of January 4 1983 Additional orphan drug amendments were passed by Congress in 1984 1985 and 1988 The use of the term orphan as in orphan drug orphan disease etc does not actually appear in the text of the law which focuses upon definitions of and treatments for rare diseases and conditions"

The 1983 Orphan Drug Act guarantees the developer of an orphan product seven years of market exclusivity following the approval of the product by the FDA As a result of the Orphan Drug Act the following procedures are administered by the Office of Orphan Products Development

- Reviewing and approving requests for orphan product designation
- Overseeing the orphan product program that gives sponsors seven years of exclusive marketing for orphan products
- Coordinating research study design assistance for sponsors of drugs for rare diseases
- Encouraging sponsors to conduct open protocols allowing patients to be added to ongoing studies
- Awarding grant funding to defray costs of qualified clinical testing incurred in connection with the development of drugs for rare diseases and conditions

The original definition of ' rare disease or condition in the Orphan Drug Act was amended in October 1984 by P L 98 551 to add a numeric prevalence threshold to the definition

> ' the term rare disease or condition means any disease or condition which (a) affects less than 200 000 persons in the U S or (b) affects more than 200,000 persons in the U S but for which there is no reasonable expectation that the cost of developing and making available in the U S a drug for such disease or condition will be recovered from sales in the U S of such drug

Prior to this revision of the Orphan Drug Act every sponsor

information regardless of the size of the proposed target patient population A product may still be designated as an orphan by demonstrating that the financial criteria of the law are applicable regardless of the number of patients affected

P L 100 290 amended the Orphan Drug Act on April 18 1988 and requires that the application for designation be made prior to the submission of an application for marketing approval New Drug Application (NDA) or Product License Application (PLA) Prior to this amendment the designation request could be filed at any time prior to FDA s approval to market the product

Section 1205 of P L 104 188 reinstated the tax credits for clinical testing expenses of orphan drugs for the period July 1 1996 to May 31 1997 and allows these credits to be carried forward/back like some other business tax credits

The Orphan Drug Final Regulations were published in the Federal Register on December 29 1992 and became effective thirty days thereafter

Orphan Drug Designation

In order for a sponsor to obtain orphan designation for a drug or biological product an application must be submitted to OOPD and the designation approved The approval of an application for orphan designation is based upon the information submitted by the sponsor A drug that has obtained orphan designation is said to have ' orphan status Each designation request must stand on its own merit Sponsors requesting designation of the same drug for the same indication as a previously designated product must submit their own data in support of their designation request The approval of an orphan designation request does not alter the standard regulatory requirements and process for obtaining marketing approval Safety and efficacy of a compound must be established through adequate and well controlled studies

Incentives of the Orphan Drug Act

The Orphan Drug Act (P L 97 414 as amended) includes various incentives that have stimulated a considerable amount of interest in the development of orphan drug and biological products These incentives include tax credits for clinical research undertaken by a sponsor to generate required data for marketing approval and seven years of marketing exclusivity for a designated drug or biological product approved by the FDA

Section 527 of the Orphan Drug Act provides a seven year period of exclusive marketing to the first sponsor who obtains marketing approval for a designated orphan drug or biological product Exclusivity begins on the date that the marketing application is approved by FDA for the designated orphan drug and applies only to the indication for which the drug has been designated and approved A second application for the same drug for a different use could be approved by FDA.

Final regulations on the tax credits were published in the Federal Register on October 3 1988 (53 FR 38708) and the current version of these regulations are in Title 26, Code of Federal Regulations Section 45c The Internal Revenue Service administers the tax credit provisions and specific questions about the interpretation of the law or regulations affecting the applicability of the tax credit provision of the Act should be directed to IRS If more information on tax credits is needed contact Pass Through and Special Industries Division Office of the Chief Counsel Internal Revenue Service 1111 Constitution Avenue NW Washington, DC 20224 telephone is (202) 622 3120

Protocol Assistance

Section 525 of the Orphan Drug Act provides for formal protocol assistance when requested by the sponsors of drugs for rare diseases or conditions The formal review of a request for protocol assistance is the direct responsibility of the Center for Drug Evaluation and Research (CDER) or the Center for Biologic Evaluation and Research (CBER) depending on which Center has authority for review of the product The Office of Orphan Products Development (OOPD) is responsible for insuring that the request qualifies for consideration under section 525 of the FFDCA. This includes determining "whether there is reason to believe the sponsor's drug is a drug for a disease or condition that is rare in the United States A sponsor need not have obtained orphan drug designation to receive protocol assistance

Once OOPD determines that the proposed compound is for a disease or condition that is rare in the U S the request will be forwarded to the responsible reviewing division for formal review and direct response OOPD monitors the review process within the respective CDER/CBER reviewing division and where possible assists in resolving specific issues that may arise during the review process It should be understood that protocol assistance provided under the Act does not waive the necessity for the submission of an Investigational New Drug Application (IND) by sponsors planning to conduct clinical trials with the product

Research Grants

The FDA, through OOPD funds the development of orphan products through its grants program for clinical studies The Request for Applications (RFA) announcing availability of funds is published in the Federal Register each year usually in June Eligibility for grant funding is extended to medical devices and medical foods for which there is no reasonable expe tation of development without such assistance Applications are reviewed by panels of outside experts and are funded by priority score

OOPD Home Page | COMMENTS | DISCLAIMER | SEARCH | FDA Home Page

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-612

MAR 19 1999

Hind Health Care, Inc
Attention Larry Caldwell, Ph.D
Consultant to Hind Health Care, Inc
3707 Williams Road Suite 101
San Jose CA 95117 2017

Dear Dr Caldwell

Please refer to your new drug application (NDA) dated May 31 1996 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Lidoderm Patch (lidocaine patch) 5% w/w Please refer to our not approvable letter dated April 17, 1997, and our approvable letter dated December 2 1998

We acknowledge receipt of your submission dated January 15 1999 This submission, together with your submissions of August 30, October 30 and December 1, 1997, February 9 1999 and March 4 1999 and correspondence via facsimile transmission dated March 15 and 18(two) 1999 constituted a complete response to our December 2 1998 action letter

This new drug application provides for the use of Lidoderm Patch (lidocaine patch) 5% w/w for the treatment of pain in post herpatic neuralgia.

We have completed the review of this application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the agreed upon labeling text. Accordingly the application is approved effective on the date of this letter

The final printed labeling (FPL) must be identical to the submitted draft labeling (package insert submitted March 4 and 18, 1999, immediate container and carton labels submitted March 15 1999) 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 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed Please individually mount ten of the copies on heavy weight paper or similar material For administrative purposes, this submission should be designated "FPL for approved NDA 20-612 " Approval of this submission by FDA is not required before the labeling is used

Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless we expect your continued cooperation to resolve any problems that may be identified.

In addition, please submit three copies of the introductory promotional materials that you propose to use for this product. All proposed materials should be submitted in draft or mock up form, not final print. Please submit 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-40
Food and Drug Administration
5600 Fishers Lane
Rockville Maryland 20857

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

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314 80 and 314 81

If you have any questions contact Victoria Lutwak, Project Manager, at (301) 827 2090

Sincerely

/S/

John E Hyde Ph.D M.D
Deputy Director
Division of Anti Inflammatory, Analgesic and
Ophthalmic Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research

cc
Archival NDA 20-612
HFD-550/Div Files
HFD-550/V Lutwak
HFD-550/ J Hyde/ C Fang/ H Patel/ C Yanw
HF 2/MedWatch (with labeling)
HFD 002/ORM (with labeling)
HFD-105/ADRA (with labeling)
HFD-40/DDMAC (with labeling)
HFD 613/OGD (with labeling)
HFD 21/ACS (with labeling) for drug discussed at advisory committee meeting
HFD 35/Orphan Drugs
HFD 95/DDMS (with labeling)
HFD 830/DNDC Division Director
DISTRICT OFFICE

Drafted by vl/March 10, 1999
Initialed by vl
final
filename v/NDA/20612/990319AP

APPROVAL (AP)

Endo
ENDO LABORATORIES

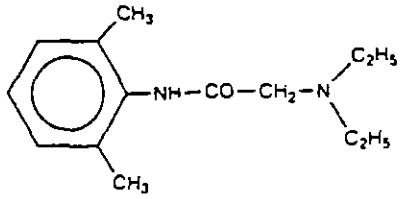
6524 00

LIDODERM®
(lidocaine patch 5%)

DESCRIPTION

LIDODERM (lidocaine patch 5%) is comprised of an adhesive material containing 5% lidocaine which is applied to a non woven polyester felt backing and covered with a polyethylene terephthalate (PET) film release liner. The release liner is removed prior to application to the skin. The size of the patch is 10 cm × 14 cm.

Lidocaine is chemically designated as acetamide, 2-(diethylamino)-N-(2,6-dimethylphenyl)-, has an octanol:water partition coefficient of 43 at pH 7.4, and has the following structure:



Each adhesive patch contains 700 mg of lidocaine (50 mg per gram adhesive) in an aqueous base. It also contains the following inactive ingredients: dihydroxyaluminum aminoacetate, disodium edetate, gelatin, glycerin, kaolin, methylparaben, polyacrylic acid, polyvinyl alcohol, propylene glycol, propylparaben, sodium carboxymethylcellulose, sodium polyacrylate, D-sorbitol, tartaric acid, and urea.

CLINICAL PHARMACOLOGY

Pharmacodynamics

Lidocaine is an amide-type local anesthetic agent and is suggested to stabilize neuronal membranes by inhibiting the ionic fluxes required for the initiation and conduction of impulses.

The penetration of lidocaine into intact skin after application of LIDODERM is sufficient to produce an analgesic effect, but less than the amount necessary to produce a complete sensory block.

Pharmacokinetics

Absorption

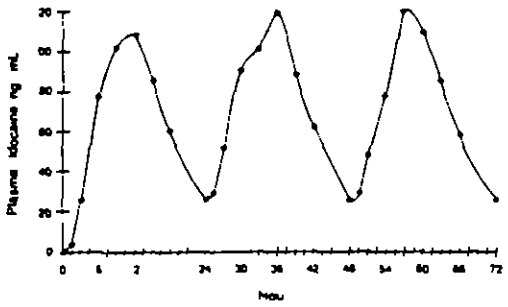
The amount of lidocaine systemically absorbed from LIDODERM is directly related to both the duration of application and the surface area over which it is applied. In a pharmacokinetic study, three LIDODERM patches were applied over a total area of 420 cm^2 of intact skin on the backs of normal volunteers for 12 hours. Blood samples were withdrawn for determination of lidocaine concentration during the application and for 12 hours after removal of patches. The results are summarized in Table 1.

Table 1
Absorption of lidocaine from LIDODERM
Normal volunteers (n = 15) 12 hour wearing time

LIDODERM Patch	Application Site	Area (cm^2)	Dose Absorbed (mg)	C_{max} (µg/mL)	T_{max} (hr)
3 patches (2100 mg)	Back	420	64 ± 32	0.13 ± 0.06	1.7 ± hr

When LIDODERM is used according to the recommended dosing instructions, only 3.2% of the dose applied is expected to be absorbed. At least 95% (665 mg) of lidocaine will remain in a used patch. Mean peak blood concentration of lidocaine is about 0.13 µg/mL (about 1/10 of the therapeutic concentration required to treat cardiac arrhythmias). Repeated application of three patches simultaneously for 12 hours (recommended maximum daily dose) once per day for three days indicated that the lidocaine concentration does not increase with daily use. The mean plasma pharmacokinetic profile for the 15 healthy volunteers is shown in Figure 1.

Figure 1
Mean lidocaine blood concentrations after three consecutive daily applications of three LIDODERM patches simultaneously for 12 hours per day in healthy volunteers (n = 15)



Distribution

When lidocaine is administered intravenously to healthy volunteers, the volume of distribution is 0.7 to 2.7 L/kg (mean 1.5 ± 0.6 SD, n = 15). At concentrations produced by application of *LIDODERM*, lidocaine is approximately 70% bound to plasma proteins, primarily alpha 1 acid glycoprotein. At much higher plasma concentrations (1 to 4 µg/mL of free base), the plasma protein binding of lidocaine is concentration dependent. Lidocaine crosses the placental and blood brain barriers, presumably by passive diffusion.

Metabolism
It is not known if lidocaine is metabolized in the skin. Lidocaine is metabolized rapidly by the liver to a number of metabolites including monoethylglycinexylidide (MEGX) and glycinexylidide (GX), both of which have pharmacologic activity similar to but less potent than that of lidocaine. A minor metabolite, 2,6-xylidine, has unknown pharmacologic activity but is a known carcinogen in rats. The blood concentration of this metabolite is negligible following application of LIDODERM (lidocaine patch 5%). Following intravenous administration, MEGX and GX concentrations in serum range from 11 to 36% and from 5 to 11% of lidocaine concentrations, respectively.

Excretion
Lidocaine and its metabolites are excreted by the kidneys. Less than 10% of lidocaine is excreted unchanged. The half-life of lidocaine elimination from the plasma following IV administration is 81 to 149 minutes (mean 107 ± 22 SD, n = 15). The systemic clearance is 0.33 to 0.90 L/min (mean 0.64 ± 0.18 SD, n = 15).

CLINICAL STUDIES
Single-dose treatment with LIDODERM was compared to treatment with vehicle patch (without lidocaine) and to no treatment (observation only) in a double-blind, crossover clinical trial with 35 post-herpetic neuralgia patients. Pain intensity and pain relief scores were evaluated periodically for 12 hours. LIDODERM performed statistically better than vehicle patch in terms of pain intensity from 4 to 12 hours.

Multiple-dose, two-week treatment with LIDODERM was compared to vehicle patch (without lidocaine) in a double-blind, crossover, clinical trial of withdrawal type design conducted in 32 patients who were considered as responders to the open-label use of LIDODERM prior to the study. The constant type of pain was evaluated but not the pain induced by sensory stimuli (dysesthesia). Statistically significant differences favoring LIDODERM were observed in terms of time to exit from the trial (14 versus 3.8 days at p-value = 0.001), daily average pain relief, and patients preference of treatment. About half of the patients also took oral medication commonly used in the treatment of post-herpetic neuralgia. The extent of use of concomitant medication was similar in the two treatment groups.

INDICATION AND USAGE
LIDODERM is indicated for relief of pain associated with post-herpetic neuralgia. It should be applied only to intact skin.

CONTRAINDICATIONS
LIDODERM is contraindicated in patients with a known history of sensitivity to local anesthetics of the amide type or to any other component of the product.

WARNINGS
Accidental Exposure in Children
Even a used LIDODERM patch contains a large amount of lidocaine (at least 665 mg). The potential exists for a small child or a pet to suffer serious adverse effects from chewing or sucking on a new or used LIDODERM patch, although the risk with this formulation has not been evaluated. It is important for patients to store and dispose of LIDODERM out of the reach of children and pets.

Excessive Dosing
Excessive dosing by applying LIDODERM to larger areas or for longer than the recommended wearing time could result in increased absorption of lidocaine and high blood concentrations, leading to serious adverse effects (see ADVERSE REACTIONS, Systemic Reactions). Lidocaine toxicity could be expected at lidocaine blood concentrations above 5 µg/mL. The blood concentration of lidocaine is determined by the rate of systemic absorption and elimination. Longer duration of application of more than the recommended number of patches, smaller patients or compromised elimination may all contribute to increasing the blood concentration of lidocaine. With recommended dosing of LIDODERM, the average peak blood concentration is about 0.13 µg/mL, but concentrations higher than 0.25 µg/mL have been observed in some individuals.

PRECAUTIONS
General
Hepatic Disease
Patients with severe hepatic disease are at greater risk of developing toxic blood concentrations of lidocaine because of their inability to metabolize lidocaine normally.

Allergic Reactions
Patients allergic to para-aminobenzoic acid derivatives (procaine, tetracaine, benzocaine, etc.) have not shown cross sensitivity to lidocaine. However, LIDODERM should be used with caution in patients with a history of drug sensitivities, especially if the etiologic agent is uncertain.

Non-intact Skin
Application to broken or inflamed skin, although not tested, may result in higher blood concentrations of lidocaine from increased absorption. LIDODERM is only recommended for use on intact skin.

Eye Exposure
The contact of LIDODERM with eyes, although not studied, should be avoided based on the findings of severe eye irritation with the use of similar products in animals. If eye contact occurs, immediately wash out the eye with water or saline and protect the eye until sensation returns.

Drug Interactions
Antiarrhythmic Drugs.
LIDODERM should be used with caution in patients receiving Class I antiarrhythmic drugs (such as tocainide and mexiletine) since the toxic effects are additive and potentially synergistic.

Local Anesthetics
When LIDODERM is used concomitantly with other products containing local anesthetic agents, the amount absorbed from all formulations must be considered.

Carcinogenesis, Mutagenesis, Impairment of Fertility
Carcinogenesis.
A minor metabolite, 2,6-xylidine, has been found to be carcinogenic in rats. The blood concentration of this metabolite is negligible following application of LIDODERM.

Mutagenesis.
Lidocaine HCl is not mutagenic in Salmonella/mammalian microsome test nor clastogenic in chromosome aberration assay with human lymphocytes and mouse micronucleus test.

Impairment of Fertility
The effect of LIDODERM on fertility has not been studied.

Pregnancy

Teratogenic Effects. Pregnancy Category B

LIDODERM (lidocaine patch 5%) has not been studied in pregnancy. Reproduction studies with lidocaine have been performed in rats at doses up to 30 mg/kg subcutaneously and have revealed no evidence of harm to the fetus due to lidocaine. There are however no adequate and well controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, LIDODERM should be used during pregnancy only if clearly needed.

Labor and Delivery

LIDODERM has not been studied in labor and delivery. Lidocaine is not contraindicated in labor and delivery. Should LIDODERM be used concomitantly with other products containing lidocaine, total doses contributed by all formulations must be considered.

Nursing Mothers

LIDODERM has not been studied in nursing mothers. Lidocaine is excreted in human milk, and the milk plasma ratio of lidocaine is 0.4. Caution should be exercised when LIDODERM is administered to a nursing woman.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

ADVERSE REACTIONS

Localized Reactions

During or immediately after treatment with LIDODERM (lidocaine patch 5%), the skin at the site of treatment may develop erythema or edema or may be the locus of abnormal sensation. These reactions are generally mild and transient, resolving spontaneously within a few minutes to hours. In clinical studies with LIDODERM, there were no serious reactions reported. One out of 150 subjects in a three-week study was discontinued from treatment because of a skin reaction (erythema and hives).

Allergic Reactions

Allergic and anaphylactoid reactions associated with lidocaine, although rare, can occur. They are characterized by urticaria, angioedema, bronchospasm, and shock. If they occur, they should be managed by conventional means. The detection of sensitivity by skin testing is of doubtful value.

Systemic (Dose-Related) Reactions:

Systemic adverse reactions following appropriate use of LIDODERM are unlikely due to the small dose absorbed (see CLINICAL PHARMACOLOGY, Pharmacokinetics). Systemic adverse effects of lidocaine are similar in nature to those observed with other amide local anesthetic agents, including CNS excitation and/or depression (light headedness, nervousness, apprehension, euphoria, confusion, dizziness, drowsiness, tinnitus, blurred or double vision, vomiting, sensations of heat, cold or numbness, twitching, tremors, convulsions, unconsciousness, respiratory depression and arrest). Excitation of CNS reactions may be brief or may not occur at all, in which case the first manifestation may be drowsiness merging into unconsciousness. Cardiovascular manifestations may include bradycardia, hypotension and cardiovascular collapse leading to arrest.

OVERDOSAGE

Lidocaine overdose from cutaneous absorption is rare, but could occur. If there is any suspicion of lidocaine overdose (see ADVERSE REACTIONS, Systemic Reactions), drug blood concentrations should be checked. The management of overdose includes close monitoring, supportive care and symptomatic treatment. Dialysis is of negligible value in the treatment of acute overdose with lidocaine.

In the absence of massive topical or erdose or oral ingestion, evaluation of symptoms of toxicity should include consideration of other etiologies for the clinical effects of overdosage from other sources of lidocaine or other local anesthetics.

The oral LD_{50} of lidocaine HCl is 459 (346-573) mg/kg (as the salt) in non-fasted female rats and 214 (159-324) mg/kg (as the salt) in fasted female rats, which are equivalent to roughly 4000 mg and 2000 mg respectively in 50 to 70 kg man based on the adult's surface area dosage conversion factors between species.

DOSAGE AND ADMINISTRATION

Apply LIDODERM to intact skin to cover the most painful area. Apply up to three patches only once for up to 12 hours within a 24 hour period. Patches may be cut into smaller sizes with scissors prior to removal of the release liner. Clothing may be worn over the area of application. Smaller areas of treatment are recommended in a debilitated patient or a patient with impaired elimination.

If irritation or a burning sensation occurs during application, remove the patch(es) and do not reapply until the irritation subsides.

When LIDODERM is used concomitantly with other products containing local anesthetic agents, the amount absorbed from all formulations must be considered.

HANDLING AND DISPOSAL

Hands should be washed after the handling of LIDODERM and eye contact with LIDODERM should be avoided. The used patch should be immediately disposed of in such a way as to prevent its access by children or pets.

HOW SUPPLIED

LIDODERM (lidocaine patch 5%) is available as the following:

NDC 63481-687-06 resealable envelope containing 5 patches (10 cm x 14 cm) box of 6 envelopes

KEEP ENVELOPE SEALED AT ALL TIMES WHEN NOT IN USE

Store at 25°C (77°F), excursions permitted to 15°-30°C (59°-86°F). [See USP Controlled Room Temperature].

Endo®

Manufactured for
Endo Pharmaceuticals Inc
Chadds Ford Pennsylvania 19317

Manufactured by
TEIKOKU SEIYAKU CO.,LTD
Sanbonmatsu Kagawa 769 2695
Japan

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Printed in Japan

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Ends Pharmaceutical, Inc

Just three days ago some-
thing wonderful happened —
Ed Odern came into my life

For 26 years I have suffered
from a very bad case of shingles
followed by severe neuralgic
pains and spasms ever so often

I have used the patches three
times now, and enjoying a
nights rest, and the relief
is a long time

Dr Ronald Mace is my doctor,
Thanks to the samples from
you folks, and prescriptions for
more I can enjoy living again

I have called all the doctors offices
to tell them of my success, hoping
to help others

Just wanted to share the
good news, keep up the good
work and God bless

(over)

Gratefully,

[redacted]