U.S. FOOD & DRUG ADMINISTRATION

FDA, Center for Veterinary Medicine Advertising & Promotion Oversight Update Food and Drug Law Institute - 2018

Thomas J. Moskal, DVM, MLIS, Dipl. ACLAM
FDA Center for Veterinary Medicine
October 17, 2018

CVM's Mission

- Protecting Human and Animal Health
  - Human Food Safety
  - Human User Safety
  - Target Animal Safety
  - Animal Drug Effectiveness – prevent indirect hazards

Overview

- Special Considerations
- Particular Concerns

Special Considerations

- Variation in Animal Patient Populations
  - Number of Species
  - Disparity in size
- Food Animals
  - Drug residues in food
  - Drug depletion not the same in all species




Recent Advisory Actions

- WL – OVAMED (altrenogest)
- UL – APOQUEL (oclacitinib tablet)
- UL – GALLIPRANT (grapiprant tablet)

OVAMED (altrenogest)


OvaMed* (altrenogest)
Your Alternative Solution
OvaMed® is a synthetic progesterone and is indicated for the suppression of estrus in mares.
OvaMed® is the first FDA-approved generic alternative to Regu-Mate®.
Proven effective
Easy to administer
Easy on the budget
OvaMed™
(altrenogest)
For more information, call us toll free at 888-524-6332 or visit bimedaequine.com
Bimeda
*Federal law restricts this drug to use by or on the order of a licensed veterinarian. FOR ORAL USE IN HORSES ONLY. Pregnant women or women who suspect they are pregnant should not handle OvaMed™. Protective gloves must be worn by all persons handling this product. Refer to the product sheet for comprehensive product information. OvaMed® is a registered trademark of Bimeda, Inc. Regu-Mate® is a registered trademark of Intervet BV. Copyright Bimeda 2017

Human risks associated with OVAMED

- Potential for fetal abnormalities
- HUMAN WARNINGS: Skin contact must be avoided. Protective gloves must be worn
- Pregnant women should not handle OVAMED
- Accidental absorption could lead to a disruption of the menstrual cycle or prolongation of pregnancy.

PEOPLE WHO SHOULD NOT HANDLE THIS PRODUCT

1. Women who are or suspect they are pregnant.

2. Anyone with thrombophlebitis or thromboembolic disorders or with a history of these events

3. Anyone with cerebral-vascular or coronary-artery disease.

4. Women with known or suspected carcinoma of the breast.

5. People with known or suspected estrogen-dependent neoplasia.

6. Women with undiagnosed vaginal bleeding.

7. People with benign or malignant tumors which developed during the use of oral contraceptives or other estrogen-containing products.

8. Anyone with liver dysfunction or disease.

APOQUEL (oclacitinib tablet)

Fast and effective

- Itch relief begins within 4 hours; effectively controls itch within 24 hours[1,5]

Safe

- Without many of the side effects associated with steroids[5]
- Can be used with many other drugs, including anti-infectives, parasiticides, antifungals, NSAIDs and allergen-specific immunotherapy[2]

Allows diagnostic testing, so you can give dogs relief and restore the quality of life while you determine the cause of the itch[2,6]

Indications

Control of pruritus associated with allergic dermatitis and control of atopic dermatitis in dogs at least 12 months of age.

APOQUEL (oclacitinib tablet)

Important Safety Information

Do not use APOQUEL in dogs less than 12 months of age or those with serious infections. APOQUEL may increase the chances of developing serious infections, and may cause existing parasitic skin infestations or pre-existing cancers to get worse. APOQUEL has not been tested in dogs receiving some medications including some commonly used to treat skin conditions such as corticosteroids and cyclosporine. Do not use in breeding, pregnant, or lactating dogs. Most common side effects are vomiting and diarrhea. APOQUEL has been used safely with many common medications including parasiticides, antibiotics and vaccines.

For more information, please see the full Prescribing Information.

apoquel (oclacitinib tablet)

MOA | EFFICACY | SAFETY | APOQUEL DOGS | DOSING | RESOURCES | SIGN IN TO PURCHASE

FDA

APOQUEL® delivers fast, safe relief from pruritus associated with any allergic dermatitis, with the versatility for long-term therapy when needed

Minimal side effects

Side effects of APOQUEL were similar to placebo without many of the side effects associated with the use of steroids[1]

Safe for long-term use

Owners reported minimal side effects in dogs that were given APOQUEL for more than 2 years in a pre-approval, observational continuation study[2]

Can be used concomitantly with many other medications

APOQUEL can be used in combination with many common therapies including vaccines, NSAIDs, antibiotics and allergen-specific immunotherapy[2]

Relieves itch while you diagnose the cause

APOQUEL does not compromise diagnostic testing, so you can restore quality of life while you determine the underlying cause of itch[3]

Fast a
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Safe
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NSAID

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APOQUEL (oclacitinib tablet)

1 - Short-term study – Cosgrove, 2013

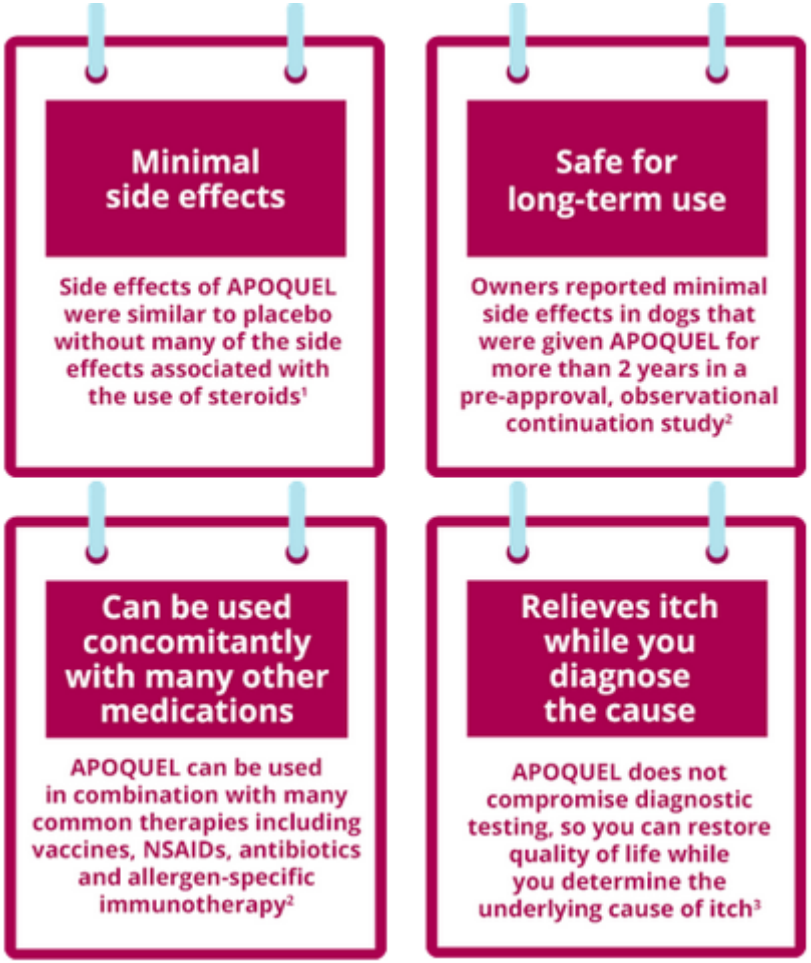
- "Side effects were similar to placebo"

2 - Long-term study – Cosgrove, 2015

- "Safe for long-term use."
- "The abnormal clinical signs reported most frequently (in ≥5% of the dogs) as a non-pre-existing finding were as follows: urinary tract infection/cystitis (11.3%), vomiting (10.1%), otitis (9.3%), pyoderma (9.3%) and diarrhea (6.1%).

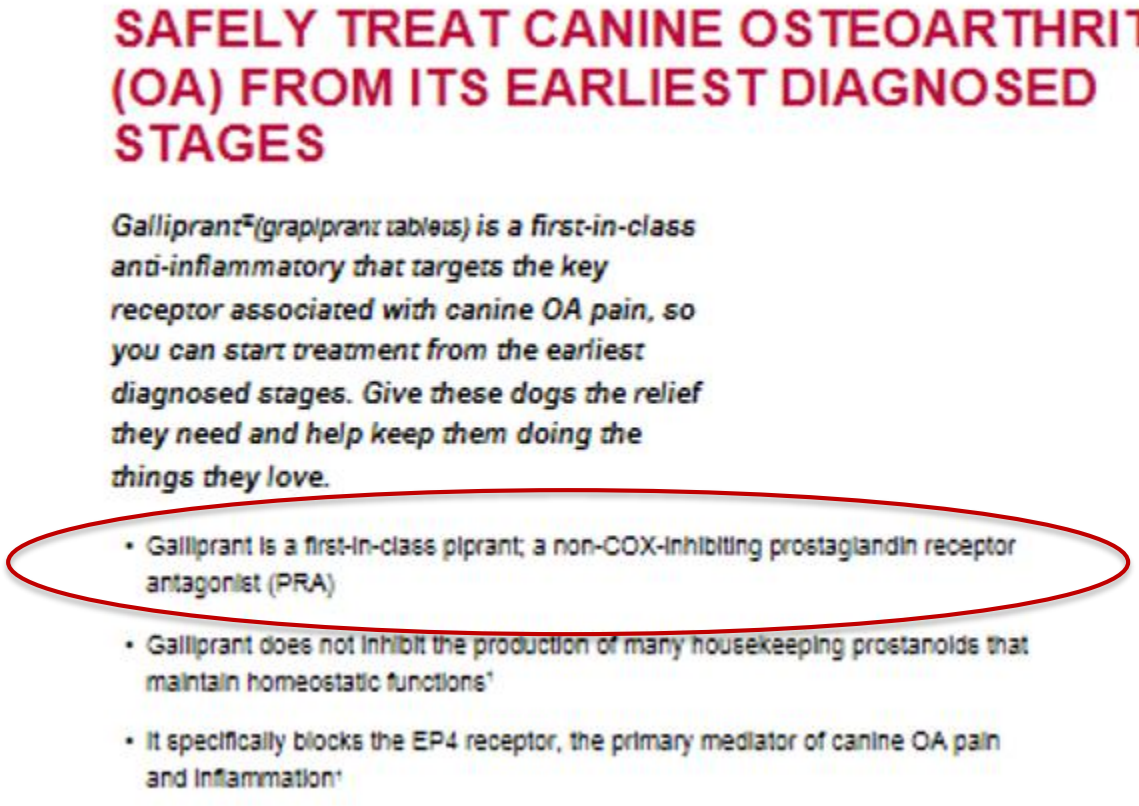
“The use of APOQUEL has not been evaluated in combination with other systemic immunosuppressive agents.”

APOQUEL (oclacitinib tablet)



GALLIPRANT (grapiprant tablets)

- Indicated for the control of pain and inflammation associated with osteoarthritis in dogs.



GALLIPRANT (grapiprant tablets)

first-in-class piprant, a non-COX-inhibiting prostaglandin receptor antagonist (PRA).

-vs-

non-cyclooxygenase (COX) inhibiting, non-steroidal anti-inflammatory drug (NSAID) in the piprant class.

Description:

GALLIPRANT® (grapiprant tablets) is a prostaglandin E_2 (PGE_2) EP4 receptor antagonist; a non-cyclooxygenase (COX) inhibiting, non-steroidal anti-inflammatory drug (NSAID) in the piprant class. GALLIPRANT is a flavored, oval, biconvex, beige to brown in color, scored tablet debossed with a "G" that contains grapiprant and desiccated pork liver as the flavoring agent.

GALLIPRANT (grapiprant tablets)

Description: GALLIPRANT (grapiprant tablets) is a prostaglandin E2 (PGE2) EP4 receptor antagonist; a non-cyclooxygenase (COX) inhibiting, non steroida anti inf ammatory drug (NSAID) in the piprant class.

TREAT WITH GALLIPRANT FROM THE EARLIEST DIAGNOSED STAGES OF CANINE OA

Mode of action targets canine OA pain and inflammation while reducing the impact on GI, kidney and liver homeostasis[1,2]

- Suitable for dogs as young as 9 months of age
- Proven safe in a 9-month safety study at up to approximately 15X the recommended therapeutic dose in healthy dogs[2,3]
- Most dogs can be dosed with a whole or half tablet

Please see important safety information below.

- Neither treatment nor GI disturbance was associated with changes in appetite, appearance or demeanor of dogs
- Suitable for dogs as young as 9 months of age

CVM Contact Information

Center for Veterinary Medicine, Division of Surveillance, HFV-210

Telephone: (240) 402-7082

Email: CVMSurveillance@fda.hhs.gov

Form FDA 2301 (drug experience reporting) and Form FDA 1932 (adverse drug experience reporting) may be obtained on the Internet at *https://www.fda.gov/AboutFDA/ReportsManualsForms/Forms/*, by telephoning the Division of Surveillance (HFV-210), or by submitting a written request to the following address: Food and Drug Administration, Center for Veterinary Medicine, Division of Surveillance (HFV-210), 7500 Standish Pl., Rockville, MD 20855-2764.

Consumers deserve truthful, balanced and non-misleading information

OPDP Update on Oversight of Prescription Drug Promotion

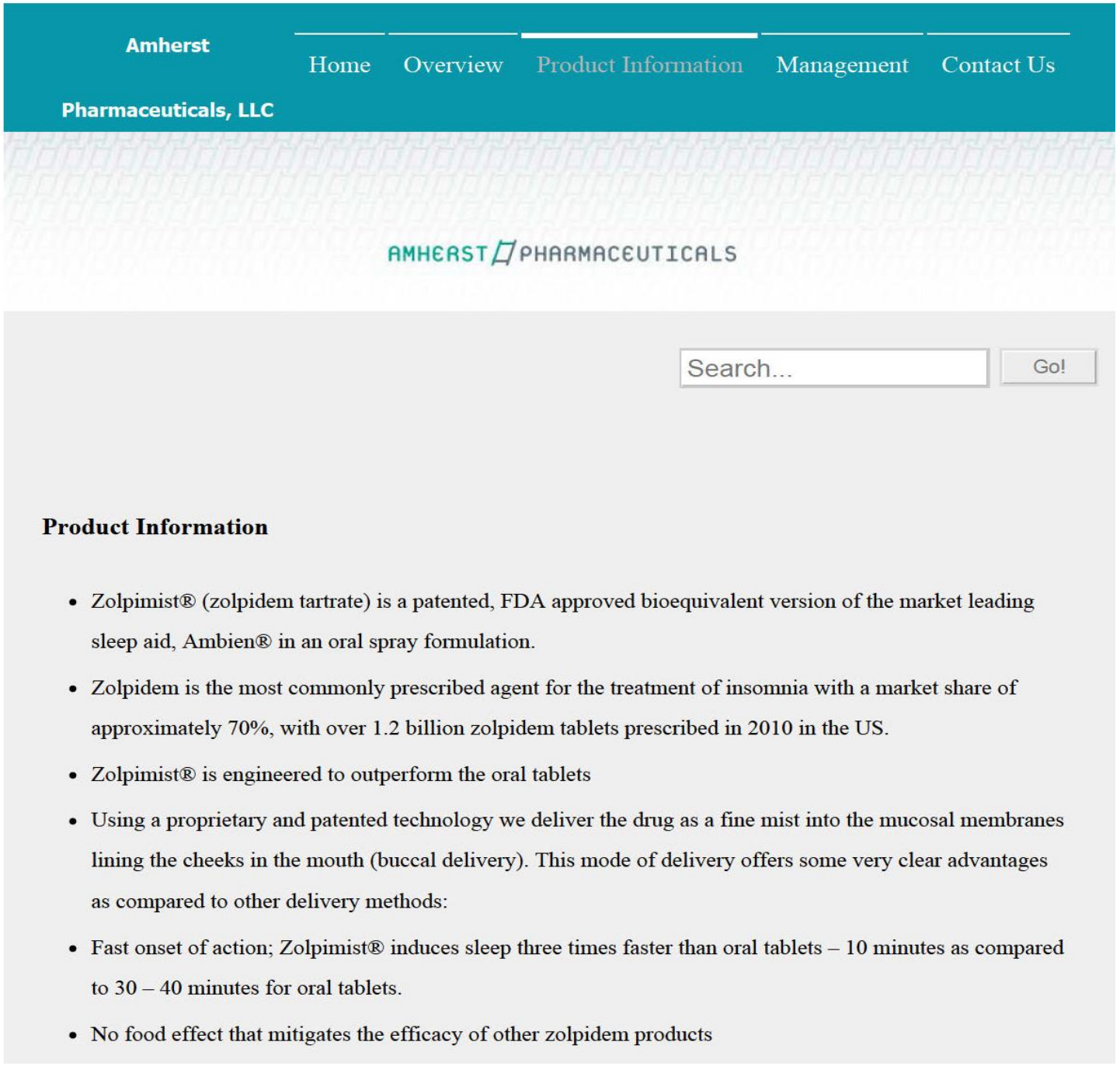
Thomas Abrams
Director
Office of Prescription Drug Promotion
Food and Drug Administration
October 17, 2018

Zolpimist Warning Letter

- Webpage and exhibit panels
- Violations include:
  - False or misleading risk presentation
  - False or misleading claims about efficacy
- 505(b)(2) product-zolpidem tartrate
  - Bioequivalent to Ambien
- Indication:
  - Indicated for the short-term treatment of insomnia characterized by difficulties with sleep initiation. Zolpidem tartrate has been shown to decrease sleep latency for up to 35 days in controlled clinical studies…. The clinical trials performed in support of efficacy were 4-5 weeks in duration with the final formal assessments of sleep latency performed at the end of treatment.

Risk Information for Zolpimist

- Warnings and precautions include:
  - CNS depressant effects and next day impairment, need to evaluate for co-morbid diagnoses, severe anaphylactic and anaphylactoid reactions, abnormal thinking and behavioral changes, use in patients with depression, respiratory depression, and withdrawal effects
- Most common adverse reactions include:
  - Drowsiness, dizziness, diarrhea, and “drugged feelings”


Amherst
Pharmaceuticals, LLC
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AMHERST PHARMACEUTICALS
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Product Information
• Zolpimist® (zolpidem tartrate) is a patented, FDA approved bioequivalent version of the market leading sleep aid, Ambien® in an oral spray formulation.
• Zolpidem is the most commonly prescribed agent for the treatment of insomnia with a market share of approximately 70%, with over 1.2 billion zolpidem tablets prescribed in 2010 in the US.
• Zolpimist® is engineered to outperform the oral tablets
• Using a proprietary and patented technology we deliver the drug as a fine mist into the mucosal membranes lining the cheeks in the mouth (buccal delivery). This mode of delivery offers some very clear advantages as compared to other delivery methods:
• Fast onset of action; Zolpimist® induces sleep three times faster than oral tablets – 10 minutes as compared to 30 – 40 minutes for oral tablets.
• No food effect that mitigates the efficacy of other zolpidem products

Omission of Risk Information

- Omission of risk information
  - The webpage and exhibit panels had no risk information about the product

Zolpimist Superiority Claims

- Using a proprietary and patented technology…. This mode of delivery offers some very clear advantages as compared to other delivery methods.
- Fast onset of action; Zolpimist induces sleep three times faster than oral tablets – 10 minutes as compared to 30-40 minutes for oral tablets.
- Zolpimist Oral Spray works so fast, patients only take when needed and may avoid nightly tablet-formulation dependency!

Food Effect Claims for Zolpimist

- Claim
  - No food effect that mitigates the efficacy of other zolpidem products
- Approved Product Labeling
  - Dosage & Administration: “The effect of Zolpimist … may be slowed by ingestion with or immediately after a meal”
  - Clinical Pharmacology: Results suggest that “as with all zolpidem products, Zolpimist … should not be administrated with or immediately after a meal”

Claims about Use of the Product

- Claims
  - Zolpidem is the mostly commonly prescribed agent for the treatment of insomnia.
  - Zolpimist is well absorbed and may facilitate all-night sleep.

- Omission of material facts from indication of Zolpimist

Indication for Zolpimist

- Indicated for the short-term treatment of insomnia characterized by difficulties with sleep initiation. Zolpidem tartrate has been shown to decrease sleep latency for up to 35 days in controlled clinical studies…. The clinical trials performed in support of efficacy were 4-5 weeks in duration with the final formal assessments of sleep latency performed at the end of treatment.

CONZIP Warning Letter

- Professional detail aid
- Indication:
  - CONZIP is an opioid agonist indicated for the management of pain severe enough to require daily around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.
  - **Limitation of Use**
    - Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses, and because of the greater risks of overdose and death with extended-release/long-acting opioid formulations, reserve CONZIP for use in patients for whom alternative treatment options (e.g., non-opioid analgesics or immediate-release opioids) are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of pain.
    - CONZIP is not indicated as an as-needed (prn) analgesic.

Risk Information for CONZIP

- Boxed warnings include:
  - Addiction, abuse, and misuse; life-threatening respiratory depression; accidental ingestion; neonatal opioid withdrawal syndrome; concomitant use with benzodiazepines and other CNS depressants
- Contraindications
- Warnings and precautions include:
  - Serotonin syndrome risk; increased risk of seizures; suicide risk; adrenal insufficiency; life-threatening respiratory depression in patients with chronic pulmonary disease or in elderly, cachectic, or debilitated patients; severe hypotension

Does Your Pain Medication Measure Up?

ConZip® CV — All Day Pain Relief.

ConZip® CV
(tramadol hydrochloride)

VERTICAL

ConZip® Measures Up

ConZip® is an opioid agonist indicated for the management of moderate to moderately severe chronic pain in adults who require around-the-clock treatment of their pain for an extended period of time.

All Day Pain Relief

ConZip® provides a novel combination of:

- ***immediate release tramadol***
- ***extended release tramadol***

Capsule Strength	Immediate-Release Tramadol	Extended-Release Tramadol
ConZip 100 mg	25 mg	75 mg
ConZip 200 mg	50 mg	150 mg
ConZip 300 mg	50 mg	250 mg

ConZip® is classified as a schedule IV controlled substance by federal regulation.

CONZIP Claims

- ConZip CIV – All Day Pain Relief
- ConZip CIV Measures Up
- ConZip is an opioid agonist indicated for the management of moderate to moderately severe chronic pain in adults who require around-the-clock treatment of their pain for an extended period of time

Omission of Material Facts

- Omission of material facts from detail aid
- Indication:
  - CONZIP is an opioid agonist indicated for the management of pain severe enough to require daily around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate
  - **Limitation of Use**
    - Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses, and because of the greater risks of overdose and death with extended-release/long-acting opioid formulations, reserve CONZIP for use in patients for whom alternative treatment options (e.g., non-opioid analgesics or immediate-release opioids) are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of pain
    - Conzip is not indicated as an as-needed (prn) analgesic

OPDP Web Resources

- OPDP Home Page
  - http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm090142.htm
- Guidances
  - http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm109905.htm#Guidances
- Social Science Research
  - https://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm090276.htm
- Warning and Untitled Letters
  - www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/EnforcementActivitiesbyFDA/WarningLettersandNoticeofViolationLetterstoPharmaceuticalCompanies/default.htm

OPDP Contact Information

- **Telephone Number**
  - 301-796-1200
- **Fax Numbers**
  - 301-847-8444
  - 301-847-8445
- **Submission Address**
  - Food and Drug Administration
    Center for Drug Evaluation and Research
    Office of Prescription Drug Promotion
    5901-B Ammendale Road
    Beltsville, MD 20705-1266


FDA
U.S. FOOD & DRUG
ADMINISTRATION

FDA Enforcement

Actions and Priorities

U.S. FOOD & DRUG ADMINISTRATION

CBER APLB

Lisa Stockbridge, Ph.D.
Branch Chief
Advertising & Promotional Labeling Branch
Division of Case Management
Office of Compliance and Biologics Quality

Advertising & Promotional Labeling Branch

- Lisa Stockbridge, Ph.D.
- Michael Brony, Pharm. D.
- Stephanie Donahoe, R.Ph., M.P.H.
- Oluchi Elekwachi, Pharm. D., M.P.H.
- Dana Jones, M.S.
- Kristine Khuc, Pharm. D.
- Alpita Popat, Pharm. D., M.B.A.
- Sonny Saini, Pharm. D., M.B.A.
- Twanda Scales, R.N.. M.S.N./Ed.

CBER Products

- Vaccines
- Coagulation Factors
- Plasma Derivatives
- Allergenic Extracts
- Human Tissue & Cellular Products (cord blood)
- Gene Therapy Products
- Biological Devices and Test Kits
- Blood Bank Products (e.g., anticoagulants)

Promotional Material

FY14 - FY18

IDELVION Untitled Letter

February 27, 2018

IDELVION is a recombinant Factor IX indicated in children and adults with Hemophilia B (Factor IX deficiency) for

- On demand treatment and control of bleeding
- Perioperative management of bleeding
- Routine prophylaxis

IDELVION Untitled Letter

IDELVION Untitled Letter

Overpromises the effect that IDELVION has on hemophiliac patients' activities and overall quality-of-life by misleadingly implying that

- Hemophiliacs taking the product can engage in moderate to dangerous high-risk activity without consequences.
- Such activities are appropriate for typical patients with hemophilia who use the product.

Contact Information

Lisa L. Stockbridge, Ph.D.
Food and Drug Administration
Center for Biologics Evaluation and Research
10903 New Hampshire Ave
WO 71 - 5056
Silver Spring, MD 20993-0002
Phone: 240-402-9095

Send all mail to the document room:

Food and Drug Administration
Center for Biologics Evaluation and Research
Document Control Center
10903 New Hampshire Ave
WO71 - G112
Silver Spring, MD 20993-0002


Thank You!


FDA
U.S. FOOD & DRUG
ADMINISTRATION

Center for Devices and Radiological Health Enforcement Update

Deborah Wolf, JD
Regulatory Counsel
Division of Premarket and Labeling Compliance
Office of Compliance
Center for Devices and Radiological Health
October 17, 2018

Relevant sections of the FD&C Act

Federal Food, Drug, and Cosmetic Act (FD&C Act);

- Section 201(h) - defines device
- Section 201(m) - defines labeling
- Section 201(n) - requires material facts in advertising and labeling
- **Section 501(f)(1) –adulteration - failure to have approved PMA or IDE**
- Section 501(i) – adulteration - investigational devices
- **Section 502(a) – misbranding - false or misleading labeling**
- **Section 502(f)(1) – adequate instructions for use**
- **Section 502(o) – misbranding - failure to notify agency of intent to introduce device into commercial distribution**
- Section 502(q) and (r) – restricted device advertising
- Section 510(k) – submission of premarket notification
- Section 513(f) – Class III by operation of law – important for intended use
- Section 515 – approval for PMA claims and designation of restricted devices
- **520(e) - restricted devices**
- 520(g) – investigational devices

Relevant Regulations

Code of Federal Regulations (CFR)

- 21 CFR 801.4 – Intended Use
- 21 CFR 801.6 – Misleading Reference to other FDA-Regulated Product
- 21 CFR 801.109 – Prescription Device Labeling
- 21 CFR 807.81 – Required Premarket Notification
- 21 CFR 807.97 – Misbranded by Reference to FDA Approval
- 21 CFR 809.10- Labeling for *in vitro* diagnostic devices
- 21 CFR 812.7 – Promotion of Investigational Devices
- 21 CFR 814.39 – Required Premarket Approval Application

GUIDANCE DEVELOPMENT

Recently Published Final Guidance Documents

- Benefit-Risk Factors to Consider When Determining Substantial Equivalence in Premarket Notifications (510(k)) with Different Technological Characteristics - Guidance for Industry and Food and Drug Administration Staff

  https://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM404773.pdf

- Appropriate Use of Voluntary Consensus Standards in Premarket Submissions for Medical Devices - Guidance for Industry and Food and Drug Administration Staff
  - https://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM077295.pdf

Recently Issued Draft Guidance Documents

- The Special 510(k) Program - Draft Guidance for Industry and Food and Drug Administration Staff
  - https://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM621682.pdf

- Consideration of Uncertainty in Making Benefit-Risk Determinations in Medical Device Premarket Approvals, De Novo Classifications and Humanitarian Device Exemptions - Draft Guidance for Industry and Food and Drug Administration Staff
  - https://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM619220.pdf

SURVEILLANCE AND ENFORCEMENT

Surveillance and Enforcement

- Inspections
- Allegations of Regulatory Misconduct
  - Complaints from many sources (competitors, physicians, consumers)
  - Provided hardcopy or via OCMedicalDeviceCo@fda.hhs.gov
- Materials disseminated to the public
  - Television
  - Radio
  - Internet
  - Brochures

Areas of Concern

- Entirely unapproved devices (no approval, clearance, exemption)
- Modified devices (formerly legally marketed but with no approval or clearance for modification)
- Unapproved/uncleared Indications or Intended Use
- Specific claims for general indications
- Comparative Claims
- Imbalance of benefit/risk information
- Combination Products

Example – Infusion Pump and Syringe (2016)

Modifications to Device

- Company modified the pump in a manner that could significantly affect safety and effectiveness:
  - a) Changed the pressure specification range from 13 psi maximum to 15 psi maximum;
  - b) Changed the flow rate specification range from 1 – 500 ml/hr. to 0.5 - 2400 ml/hr.; and
  - c) Developed and marketed a different version of the infusion pump that uses a different syringe volume, pumping mechanism and mode of operation.

Changed Intended Use

- Original clearance:
  - *intended for use in the home setting or hospital environment using any intravenous fluids recommended for use with such syringes as ….*
  - *is not indicated for the delivery of blood or blood products."*

- Promoted device for the infusion of prescribed liquid medicines including Immunoglobulin G (IgG,) antibiotics, Desferal, pain medications, chemotherapeutics and cardiac medications.

- Indicating the device for a different route of administration or for specific medications or classes of medications raises new scientific review questions, as such changes introduce new risks that are not normally associated with the cleared indication.

Continued…

- Subcutaneous Safety Needle Sets were cleared as being "… *intended for the delivery of medication to the subcutaneous tissue.*"

- *Marketed in consumer brochure for* subcutaneous Immunoglobin (SCIg) infusion.

- **During the review, the intended use for SCIg infusion was *specifically not covered* by the cleared intended use because company was unable to supply the requested performance data.**

- Promoting for use with infusions explicitly not covered in cleared indication falls outside the cleared intended use. Indicating the device for a different route of administration raises new questions of safety and effectiveness.

Misbranding

Standard Charge Language

- …misbranded under section 502(o) of the Act, 21 U.S.C. § 352(o), because you did not notify the agency of your intent to introduce these devices into commercial distribution in that a notice or other information respecting the significant modifications to these devices and their new intended use was not provided to the FDA as required by section 510(k) of the Act, 21 U.S.C. § 360(k), and 21 C.F.R. 807.81(a)(3)(i) and (ii).

Adulteration

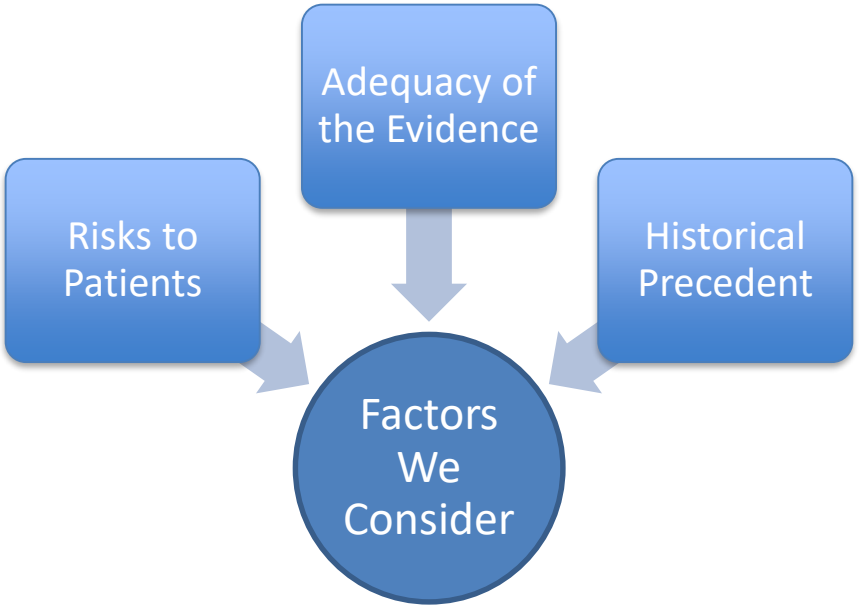
Standard Charge Language

- Adulterated under section 501(f)(1)(B) of the Act, 21 U.S.C. § 351(f)(1)(B), because these devices are class III devices under section 513(f) of the Act, 21 U.S.C. § 360c(f), and you do not have an approved application for premarket approval (PMA) in effect as required by section 515(a) of the Act, 21 U.S.C. § 360e(a), or an approved application for an investigational device exemption (IDE) under section 520(g) of the Act, 21 U.S.C. § 360j(g).

Allegations Handling

If available, include the following:

- Allegation
- Firm name and address
- Promotional materials



Reporting Allegations

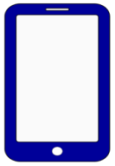
Ways to Report Allegations of Regulatory Misconduct

Regular Mail

Email

OCMedicalDeviceCo@fda.hhs.gov

Phone



240-402-7675

Online Form

Allegations of Regulatory Misconduct Form

Attention: Office of Compliance
Center for Devices and
Radiological Health
Food and Drug Administration
WO Bldg. 66 RM 3523
10903 New Hampshire Ave
Silver Spring, MD 20993

DPLC Contact Information

- **Telephone Number**

  301-796-5770

- **Fax Number**

  301-847-3138

- **Submission Address**

  Division of Premarket and Labeling Compliance
  Office of Compliance
  Center for Devices and Radiological Health
  10903 New Hampshire Avenue
  Silver Spring, MD 20993

Contact

Deborah Wolf

deborah.wolf@fda.hhs.gov

301-796-5732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