Elanco Animal Health
2500 Innovation Way
Greenfield, IN 46140
USA

RISK MINIMIZATION ACTION PLAN (RiskMAP)

Recuvyra® (fentanyl) transdermal solution

NADA 141-337

January 2016

Executive Summary

Recuvrya® (fentanyl) is a transdermal solution intended for topical application that provides systemic delivery of a potent analgesic opioid for the control of postoperative pain associated with surgical procedures in dogs. Once applied to the skin of dogs, RECUVYRA solution is a rapid drying formulation resulting in deposition of fentanyl in the stratum corneum. The dosage of RECUVYRA is 1.2 mg/lb (2.7 mg/kg) applied topically to the dorsal scapular area 2 to 4 hours prior to surgery. A single application provides analgesia for 4 days although opioid effects, including adverse events, may last for 7 days beyond administration in some dogs.

There are known human and animal risks associated with RECUVYRA that may occur in the hospital as well as following release from the hospital for home care after surgery. To minimize known risks of RECUVYRA while preserving benefits, RECUVYRA is distributed under a Risk Minimization Action Plan (RiskMAP). The specific risks associated with the use of RECUVYRA are: 1) abuse and misuse of RECUVYRA; 2) human adverse events in hospital staff that handle and apply RECUVYRA prior to surgery or interact with the application site of RECUVYRA-treated dogs following surgery; 3) human adverse events in children by interacting with the application site after RECUVYRA-treated dogs are discharged for home care following surgery; 4) human adverse events in adults by interacting with the application site after RECUVYRA-treated dogs are discharged for home care following surgery; 5) severe adverse events in dogs because of medication errors; 6) severe adverse events in dogs due to failure to recognize prolonged lack of food and water intake and sedation; 7) prolonged monitoring and hospitalization; and 8) severe adverse events in other veterinary species due to extra-label use.

To minimize known risks of RECUVYRA while preserving benefits, the goals of this RiskMAP are to: 1) prevent RECUVYRA diversion and human drug abuse; 2) prevent human adverse reactions in hospital staff that handle and apply RECUVYRA to dogs; 3) prevent human adverse reactions, especially in children, after discharging dogs for home care following surgery; 4) prevent RECUVYRA medication errors in the hospital; and 5) minimize severe adverse events in RECUVYRA-treated dogs and in species other than dogs.

To achieve the goals of this RiskMAP, several specific tools have been implemented. These include: training and certification, restricted distribution, documenting purchase patterns, enhanced adverse event reporting, and targeted communication to the veterinary medical community. In order to evaluate the effectiveness of these tools in achieving the RiskMAP goals, an evaluation plan is in place to periodically assess outcomes and includes data on human and animal safety as well as diversion, misuse and abuse of RECUVYRA. This information had been analyzed quarterly by an external review board and submitted as a RiskMAP Progress Report. Under the current RiskMAP implemented in January 2016, this information will be analyzed semi-annually by the external review broad and submitted semi-annually as a RiskMAP Progress Report. This information will be used to determine whether any adjustments or additions to this RiskMAP are indicated.

Table of Contents

Background

Recuvrya® (fentanyl) is a transdermal solution intended for topical application that provides systemic delivery of a potent analgesic opioid for the control of postoperative pain associated with surgical procedures in dogs. Once applied to the skin of dogs, RECUVYRA solution is a rapid drying formulation resulting in deposition of fentanyl in the stratum corneum. The dosage of RECUVYRA is 1.2 mg/lb (2.7 mg/kg) applied topically to the dorsal scapular area 2 to 4 hours prior to surgery. A single application provides analgesia for 4 days although opioid effects, including adverse events, may last for 7 days beyond administration in some dogs.

There are known human and animal risks associated with RECUVYRA that may occur in the hospital as well as following release from the hospital for home care after surgery. To minimize known risks of RECUVYRA while preserving benefits, RECUVYRA is distributed under a Risk Minimization Action Plan (RiskMAP). The specific risks associated with the use of RECUVYRA are: 1) abuse and misuse of RECUVYRA; 2) human adverse events in hospital staff that handle and apply RECUVYRA prior to surgery or interact with the application site of RECUVYRA-treated dogs following surgery; 3) human adverse events in children by interacting with the application site after RECUVYRA-treated dogs are discharged for home care following surgery; 4) human adverse events in adults by interacting with the application site after RECUVYRA-treated dogs are discharged for home care following surgery; 5) severe adverse events in dogs because of medication errors; 6) severe adverse events in dogs due to failure to recognize prolonged lack of food and water intake and sedation; 7) prolonged monitoring and hospitalization; and 8) severe adverse events in other veterinary species due to extra-label use. Each of these risks is briefly described below.

Abuse and misuse: Recuvyra® (fentanyl) transdermal solution contains fentanyl, a μ-opioid receptor agonist, in a high concentration (50 mg/mL) and is a Class II controlled substance with high potential for abuse similar to hydromorphone, methadone, morphine, oxycodone, and oxymorphone. Class II controlled substances have the highest potential for human abuse and criminal diversion. The high concentration of fentanyl in RECUVYRA may be a particular target for human abuse. Fentanyl has additive CNS depressant effects when used with alcohol, other opioids, or illicit drugs that cause central nervous system depression. Fatal fentanyl overdoses in humans are due to respiratory depression. The risk of abuse by humans should be considered when storing, administering, and disposing of RECUVYRA. Persons at increased risk for opioid abuse include those with a personal or family history of substance abuse (including drug or alcohol abuse or addiction) or mental illness (suicidal depression). Distribution of RECUVYRA will be limited to trained and certified distributors. These distributors will restrict sales to veterinarians who have been certified by training and have a current DEA license. RECUVYRA will not be available through retail pharmacy outlets. To minimize the risk of diversion of expired vials (partial or full), such vials be returned to a DEA registered reverse distributor for destruction.

Human adverse events in hospital staff that handle and apply RECUVYRA or interact with the application site of RECUVYRA-treated dogs following surgery*:* RECUVYRA is 1000X more concentrated than injectable fentanyl formulations approved for use in humans; a single 10 mL vial contains 500 milligrams of fentanyl.

Human adverse events in children by interacting with the application site after RECUVYRA-treated dogs are discharged for home care following surgery*:* Oral contact in children within 72 hours (3 days) of application could result in potential adverse reactions associated with systemic fentanyl blood levels including weakness or dizziness, pinpoint pupils, cold and clammy skin, weak pulse, fainting or slow breathing. Owners must be informed of these risks orally and in writing (client information sheet) prior to the administration of RECUVYRA.

Human adverse events in adults by interacting with the application site after RECUVYRA-treated dogs are discharged for home care following surgery: Oral contact in adults within 72 hours (3 days) of application should be avoided. Owners must be informed of these risks orally and in writing (client information sheet) prior to the administration of RECUVYRA.

Severe adverse events in dogs because of medication errors: RECUVYRA is 1000X more concentrated than injectable fentanyl formulations approved for use in humans; a single 10 mL vial contains 500 milligrams of fentanyl. As a result, accidental parenteral injection of RECUVYRA to dogs could result in severe adverse reactions.

Severe adverse events in dogs due to failure to recognize prolonged lack of food and water intake and sedation: Individual dogs especially sensitive to the effects of fentanyl may develop gastrointestinal stasis with an increased risk of bacterial overgrowth, accompanied by pronounced sedation, and decreased intake of food and water. Dehydration and elevations in hematocrit, albumin, and fibrinogen may occur. Feces, if present, could be soft and contain blood. Serious adverse reactions, including death, can occur if prolonged lack of food and water intake and sedation are not accompanied by supportive care. These adverse reactions can appear following discharging dogs to owners for home care.

Prolonged monitoring and hospitalization: Administration of RECUVYRA to dogs may result in severe side effects, especially in those sensitive to the effects of fentanyl. Dogs may need longer post-surgical monitoring because of hypothermia or prolonged sedation. Prolonged physiological effects (sedation, respiratory depression, hypothermia, bradycardia, and hypotension) and some clinical effects (diarrhea, vomiting, and anorexia) may occur lasting longer than 24 hours. Moderate or greater sedation can last up to 2 days after dosing. Serious adverse reactions, including death, can occur if prolonged lack of food and water intake and sedation are not accompanied by supportive care. Owners must be informed of these risks orally and in writing (client information sheet) prior to the administration of RECUVYRA.

Severe adverse events in other veterinary species due to extra-label use: Safe and effective concentrations of fentanyl are dependent on appropriate absorption from skin, and the absorption characteristics of skin vary greatly between species. The safety of RECUVYRA in cats, horses, or other species has not been evaluated. RECUVYRA must not be administered to any other

species; it is intended for use in dogs only. Reversal with naloxone or other supportive measures following administration of RECUVYRA to species, other than dogs, has not been studied.

Goals and Objectives

To minimize known risks of RECUVYRA while preserving benefits, the goals of this RiskMAP are to: 1) prevent RECUVYRA diversion and human drug abuse; 2) prevent human adverse reactions in hospital staff that handle and apply RECUVYRA to dogs; 3) prevent human adverse reactions, especially in children, after discharging dogs for home care following surgery; 4) prevent RECUVYRA medication errors in the hospital; and 5) minimize severe adverse events in RECUVYRA-treated dogs and species other than dogs.

Strategy and Tools

As the drug sponsor Elanco[1] has legal responsibility for all post-approval activities for RECUVYRA, including the RiskMAP. To achieve the goals of this RiskMAP, several tools have been implemented. The specific tools used to achieve the goals of the RiskMAP include:

- Training and Certification
- Restricted Distribution
- Documenting Purchase Patterns
- Enhanced Adverse Event Reporting
- Targeted Communication to the Veterinary Medical Community

1. Training and Certification

To achieve the goals of this RiskMAP, one of the tools is to provide specific training to veterinarians and staff. Professional detailing, training, and certification specific to RECUVYRA is administered by Elanco as a presentation in PowerPoint format (Attachment 1). The objective of the training is to educate veterinarians and staff about potential animal and human safety outcomes and risk mitigation measures so that RECUVYRA is used in a safe and effective manner. Before purchase, clinic staff that will handle or apply RECUVYRA must have documented training and certification in its use.

Training emphasizes several key topics which veterinarians and staff that purchase and handle RECUVYRA must understand in order to achieve the goals of this RiskMAP. These include:

- Abuse and misuse potential.
- Risk and danger associated with human exposure, especially in children.

[1] Elanco is the drug sponsor for the purposes of the Federal Food, Drug, and Cosmetic Act (21 CFR §514.80) and its implementing regulations. Elanco is not a distributor as defined under the Controlled Substances Act (21 CFR §802).

- What to do in the event of human exposure, especially in children.
- RECUVYRA is 1000x more potent than injectable fentanyl formulations approved for use in humans.
- Vial appearance. The RECUVYRA vial is similar in appearance to a vial for an injectable product; it should be stored away from other products in order to minimize the potential for medication error, such as administering by the incorrect route (e.g. parenteral instead of topical), improper technique of administration, and accidental overdose.
- RECUVYRA is for topical application only. It is not to be injected, which could lead to severe adverse reactions, including death, due to the potency of the product.
- To minimize the potential for medication errors, RECUVYRA should be stored as an intact kit; the components should not be separated.
- The specialized syringes that accompany the product must be used in order to minimize the potential for human exposure and medication errors; other commercially available syringes may stick or fail upon administration.
- RECUVYRA is only to be used in dogs. Safety and effectiveness in other species has not been demonstrated.
- RECUVYRA is used as a one-time only dose.
- Client counseling needs to be in both oral and written forms prior to the application of RECUVYRA, and documented by signature of the Client Information Sheet.
- Potential side effects such as profound sedation may occur in sensitive dogs, as well as GI stasis and bacterial overgrowth, which could lead to a prolonged hospital stay for these patients.
- Veterinarians should report all adverse events including human exposure, exposure in species other than the target animal, and medication errors regardless of patient outcome.
- The veterinarian should be advised to have naloxone on hand when purchasing this product.
- Summary of Distributor training and requirements.

In order to become certified to purchase and handle RECUVYRA, each veterinarian and staff member responsible for its appropriate handling and use must complete the training. As a condition of certification, it must be understood that RECUVYRA is only available through a RiskMAP program and those certified must comply with the program requirements. By signature, those completing training will confirm that they: 1) have read and understand the content of the training; 2) verify that their clinic performs orthopedic and/or soft tissue surgeries; 3) recognize that RECUVYRA is a highly abusable controlled substance and is subject to potential misuse and diversion; 4) acknowledge that they may not distribute RECUVYRA to any other DEA registrant or non-qualified facility; 5) acknowledge that RECUVYRA is intended to be used in-hospital and is not for dispensing to the client; 6) acknowledge that two people must be present at the time of administration; 7) agree to report all adverse events including

medication errors such as wrong route of administration, improper technique of administration, and accidental overdose as well as all incidents of human exposure; and 8) acknowledge that there is concern for human (especially children) exposure and will take the recommended precautions in the hospital (wearing proper attire for administration of the product) and discuss safety in the home with the client before discharge. Periodic retraining and recertification is required (every two years). Compliance monitoring will be directed by and executed by Elanco.

2. Restricted Distribution

As a product containing a Class II controlled substance, RECUVYRA is part of a closed distribution system and subject to stringent controls under the Controlled Substances Act from its manufacture through distribution to the end user. These controls include security, record keeping, reporting, order forms, and limits. RECUVYRA will only be available through a limited number of distributors that are trained and certified by Elanco (Attachment 4). These distributors will restrict sales to veterinarians who have been certified by completing training (Attachment 1) and have a current DEA license. RECUVYRA will not be available through retail pharmacy outlets. Elanco will maintain a list of veterinarians and veterinary clinics that have documented that they have the facilities for orthopedic and/or soft tissue surgery through completing training for the use of RECUVYRA. Distributors will confirm that the veterinarian has successfully completed training prior to shipping.

3. Documenting Purchase Patterns

In order to prevent diversion of RECUVYRA, the DEA registrant will monitor orders to establish baseline ordering patterns for each customer. These patterns will then be used to establish the parameters for the Suspicious Ordering Monitoring System which is currently operated by distributors of CII controlled substances. Any Suspicious Order will be held by the distributor until the legitimacy of the sale can be established. New customers will be carefully scrutinized utilizing the "Know your customer" principle to ensure that only orders from properly registered, trained, certified and DEA licensed veterinarians are filled.

4. Enhanced Adverse Event Reporting

Elanco will maintain an enhanced level of adverse event reporting. A validated reporting system will be used to supply periodic (non-serious) adverse drug events electronically to the FDA Center for Veterinary Medicine at least monthly, as well as electronic transmission of 3 day and 15 day reportable adverse events in accordance with 21 CFR §514.80. All medication errors regardless of patient outcome (e.g. incorrect route of administration), human exposures, and administration to the wrong species will be reported at least monthly. This method of reporting will accelerate the review and assessment of any events that may occur.

5. Targeted Communication to the Veterinary Medical Community

Coincident with RECUVYRA launch, Elanco sent letters to veterinarians and related providers regarding the potential risks of RECUVYRA, the training and certification requirements, information about the RiskMAP and any other tools to help assure safe use of the product

(Attachment 5). Additional communication has been and will continue to be sent regarding updates to the RiskMAP or any other key animal or human safety information.

Evaluation Plan

In order to evaluate the effectiveness of the RiskMAP in achieving its goals, an evaluation plan is in place to periodically assess outcomes.

Elanco will monitor any safety, diversion, and abuse of RECUVYRA to evaluate the effectiveness of the RiskMAP and the impact on legitimate availability. This information will be used to determine whether any adjustments or additions to this RiskMAP are indicated. Items monitored will include data on human and animal safety, diversion, misuse, and abuse of RECUVYRA.

This information will be analyzed semi-annually by an external review board composed of practicing veterinarians, former federal and/or state law enforcement personnel, epidemiology experts, and others. The review board will advise Elanco on the effectiveness of the RiskMAP and review assessments for submission to FDA as a RiskMAP Progress Report. The assessments will be submitted semi-annually.

Attachment 1: Training and Certification

Attachment 2: Package Insert (Label)

Attachment 3: Client Information Sheet

Attachment 4: Distributor Training

Attachment 5: Professional Letter