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**RE: NDA 022324 Remoxy (oxycodone) Extended-Release Capsules  
MA 5  
(b) (4) PTI-821 (oxycodone) Controlled-Release Capsules  
MA 3**

Dear Dr. McIntyre and Dr. Marsman:

The Office of Prescription Drug Promotion (OPDP) of the U.S. Food and Drug Administration (FDA) has reviewed presentations on the websites of Durect Corporation and Pain Therapeutics, Inc. regarding Remoxy (oxycodone) Extended-Release Capsules (Remoxy ER).<sup>1</sup> These websites suggest that Remoxy ER, an investigational new drug, is safe and effective for the purposes for which it is being investigated or otherwise promote the drug. As explained further below, based on these websites, Remoxy ER does not comply with the provisions of 21 CFR 312.7 and, therefore, does not qualify for the exemption for investigational drugs from certain provisions of the Federal Food, Drug, and Cosmetic Act (FD&C Act).

## Background

Remoxy ER is a new drug for which there is currently no marketing authorization in effect under section 505 of the FD&C Act or section 351 of the Public Health Service Act (PHS Act). Pain Therapeutics resubmitted a new drug application on March (b) (4) 2016, for Remoxy ER, referencing (b) (4). Statements on the Durect website, described below, indicate that Remoxy ER is an opioid drug intended for use in “long-term pain control.”<sup>2</sup> Opioids are highly addictive controlled substances that can cause death.

<sup>1</sup> <http://www.durect.com> (last accessed September 8, 2016) and <http://www.paintrials.com> (last accessed September 8, 2016). As both companies publically acknowledge, Durect and Pain Therapeutics have entered into an agreement providing Pain Therapeutics the exclusive rights to commercialize and develop Remoxy ER, based on Durect’s technology. Under the agreement, in addition to upfront and milestone payments, Durect would receive royalties for Remoxy ER, when commercialized, depending on sales volume. See e.g., <http://www.durect.com/investors/collaborations/>; <http://investor.paintrials.com/releasedetail.cfm?ReleaseID=970497>.

<sup>2</sup> Similarly, the website of Pain Therapeutics identifies Remoxy ER as an oxycodone product that “is a strong

An investigational new drug that complies with FD&C Act section 505(i) and regulations thereunder is exempt from the premarket approval requirements of section 505 (21 USC 355(i)). Additionally, 21 CFR 201.115(b) provides that an investigational new drug that “complies with section 505(i) . . . and regulations thereunder,” is exempt from the requirement of adequate directions for use in section 502(f)(1) of the Act.<sup>3</sup> 21 CFR 312.7, one of several regulations promulgated under FD&C Act section 505(i), provides that:

A sponsor or investigator, or any person acting on behalf of a sponsor or investigator, shall not represent in a promotional context that an investigational new drug is safe or effective for the purposes for which it is under investigation or otherwise promote the drug. This provision is not intended to restrict the full exchange of scientific information concerning the drug, including dissemination of scientific findings in scientific or lay media. Rather, its intent is to restrict promotional claims of safety or effectiveness of the drug for a use for which it is under investigation and to preclude commercialization of the drug before it is approved for commercial distribution.

## Discussion

Presentations about Remoxy ER that suggest that Remoxy ER is safe and/or effective for the purposes for which it is being investigated or otherwise promote the drug include the following:

On the Durect website main webpage, [www.durect.com](http://www.durect.com), information about Remoxy ER appears on a rotating basis with information about other products. The presentation on the Durect main webpage includes a photograph of white capsules with the accompanying text, “REMOXY® ER -- A unique long-acting, tamper-resistant formulation of oxycodone based on DURECT’s ORADUR® technology” and provides a clickable link inviting web visitors to “LEARN MORE.” (Clicking on any part of this presentation links directly to the specific product webpage for Remoxy ER, discussed further below.) The statements about the product on this page — including that it is “long-acting” and “tamper-resistant”— are phrased as established facts. Therefore, this presentation suggests that the product is safe and effective with the characteristics described or otherwise promotes the drug.

Additionally, nothing in this presentation, which identifies the product by the trade name under which the NDA indicates Pain Therapeutics intends to commercially market the product, discloses that this product is an investigational new drug, not authorized for marketing in the U.S. for any indication, and the presentation is thereby misleading.

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painkiller.” <http://www.paintrials.com/remoxy.html> (last accessed September 8, 2016)

<sup>3</sup> All drugs are subject to misbranding provisions under the FD&C Act<sup>3</sup>, including a requirement for labeling to bear adequate directions for use under section 502(f)(1). *Adequate directions for use* means directions under which the layman can use a drug safely and for the purposes for which it is intended. 21 CFR 201.5. However, no adequate directions for lay use can be written for a drug that requires a prescription (see section 503(b)(1)(A) of the FD&C Act)--such drugs must adhere to the terms of a regulatory exemption from 502(f)(1) in order to avoid being misbranded. Because Remoxy ER is a drug for which supervision by a licensed practitioner, and thus dispensing by prescription is required, it must satisfy one of the applicable regulatory exemptions to avoid misbranding under section 502(f)(1).

As mentioned, clicking on any part of the rotating Remoxy ER presentation on the Durect website main webpage links directly to a specific product webpage devoted entirely to Remoxy ER.<sup>4</sup>

The Remoxy ER product webpage begins with the major heading “PRODUCTS” in a very large, colorful graphic banner, followed vertically with a presentation beginning with the following (bolded emphasis original) (relative font sizes not portrayed):

## **REMOXY® ER (ORADUR® - Oxycodone)**

### **Product Overview**

Based on DURECT’s ORADUR technology, REMOXY ER is a unique long-acting formulation of oxycodone designed to discourage common methods of tampering associated with opioid misuse and abuse. It is intended for patients with moderate-to-severe chronic pain.

When taken as prescribed, opioid analgesics allows individuals suffering from chronic pain to sufficiently control their pain and resume many of their daily activities. However, this class of drugs may be abused, misused, and diverted, which has led to a major public healthcare crisis.

Continuing vertically down the Remoxy ER product webpage, there are several additional headings that expand on clicking to reveal additional statements. Only one such expanded set of content can be viewed at a time. Under the first of these headings, “Potential Benefits,” the presentation states:

- Effective long-term pain control with the convenience of twice-daily dosing
- Proprietary formulation with several properties designed to deter abuse by the most common methods (snorting, smoking, injecting, chewing, and dissolving in drinks)

The prominent claims under the Product Overview and Potential Benefits headings on this Remoxy ER product webpage suggest that Remoxy ER is safe and/or effective for the purpose for which it is being investigated or otherwise promote the drug as having several properties to deter abuse by multiple specified routes and as providing “long-term pain control” of “moderate-to-severe chronic pain.”

Additionally, the presentation on the Remoxy ER product webpage, which identifies the product by the trade name under which the NDA indicates Pain Therapeutics intends to commercially market the product, does not clearly convey that this product is an investigational new drug, not authorized for marketing in the U.S. for any indication, and is thereby misleading.

We acknowledge that the Remoxy ER product webpage includes the heading “IN DEVELOPMENT” in the local navigation sidebar on the left hand side of the page, and uses the term “Potential” preceding the term “Benefits” in a heading. The webpage also includes a third

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<sup>4</sup> <http://www.durect.com/products/development/remoxy/> (last accessed September 8, 2016)

expandable section, following “Potential Benefits” and “Commercial Opportunity,” under the heading of “Current Status.” When clicked, that section expands to make visible the following:

In March 2016, Pain Therapeutics resubmitted the NDA for REMOXY ER. In April 2016, the FDA deemed the NDA sufficiently complete to permit a substantive review, and stated that September 25, 2016 would be the target action date under the Prescription Drug User Fee Act (PDUFA).

However, this indirect statement that the product is not approved — the most information the webpage provides on this point — is only visible to website visitors on the product webpage who make the effort to expand the “Current Status” heading, and even then, the statement cannot be viewed at the same time as the prominent assertions regarding Remoxy ER’s properties that are viewed under the “Potential Benefits” heading that precedes the “Current Status” heading. In total, these presentations neither adequately convey that the product is unapproved, nor sufficiently mitigate impressions conveyed by the design of, and claims on, the webpage, such as those noted above, that Remoxy ER is safe and effective for “moderate-to-severe chronic pain” and has several properties to deter abuse by multiple routes of administration.

In addition to the presentations on the Durect website, Pain Therapeutics’ website contains presentations that similarly suggest that Remoxy ER is safe and/or effective for the purposes for which it is being investigated or that otherwise promote Remoxy ER, such as “Remoxy resists injection or snorting.”<sup>5</sup>

As noted, Pain Therapeutics has submitted an NDA for Remoxy ER, indicating the intent to begin widespread commercial distribution of the product in the near term. Conclusory statements regarding safety and effectiveness of a drug, made while an application for the product is under review, suggest an effort to shape public impressions of the drug in the lead-up to its launch, before FDA’s evaluation of the product is complete and reflected in approved drug labeling. Such statements raise considerable public health concerns and may remain probative evidence later when a product is in broad distribution. The statements are particularly irresponsible and alarming with respect to an opioid drug product.

The current opioid abuse epidemic is a critical public health matter. FDA encourages the development of abuse-deterrent opioid formulations to help combat this opioid epidemic, consistent with the FDA’s Guidance for Industry.<sup>6</sup> But Remoxy ER has not obtained approval at this time, and the representations in these websites that Remoxy ER can deter abuse by multiple routes directly implicate the product attributes that remain under review by FDA in NDA 022324, to determine whether they are supported, and if so, with what limitations or further explanation. In fact, for each of the seven extended-release/long-acting (ER/LA) opioids that FDA has, to date, approved with labeling describing the particular abuse-deterrent properties established for that product, labeling has included additional information not presented on the websites for Remoxy ER addressed above, to clarify that even where abuse deterrent properties do exist, opioid drugs such as oxycodone still expose users to the risks of addiction, abuse, and misuse. The websites described above present the purported benefits of Remoxy ER but do not address these or other

<sup>5</sup> <http://www.paintrials.com/remoxy.html> (last accessed September 8, 2016)

<sup>6</sup> Guidance for Industry, Abuse-Deterrent Opioids – Evaluation and Labeling, April 2015, available at <http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm334743.pdf>.

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risks of the product—risks that must be disclosed in advertising and promotional labeling for approved opioid drugs to ensure that those materials are not false or misleading.<sup>7</sup>

### Conclusion and Requested Action

For the reasons discussed above, Remoxy ER does not comply with the provisions of 21 CFR 312.7 and, therefore, does not qualify for the exemption for investigational drugs from certain requirements of the FD&C Act. Please submit a written response to this letter on or before September 22, 2016, stating how you intend to ensure compliance with the FD&C Act and its implementing regulations, such as explaining plans for discontinuance of materials such as those identified in this letter.

Please direct your response to the undersigned at the **Food and Drug Administration, Center for Drug Evaluation and Research, Office of Prescription Drug Promotion, Division of Professional Drug Promotion, 5901-B Ammendale Road, Beltsville, Maryland 20705-1266**. To ensure timely delivery of your submissions, please use the full address above and include a prominent directional notation (e.g. a sticker) to indicate that the submission is intended for OPDP. Please refer to NDA 022324, MA 5 and (b) (4) MA 3 in addition to the NDA (b) (4) in all future correspondence relating to this particular matter. OPDP reminds you that only written communications are considered official.

Sincerely,

{See appended electronic signature page}

Koung Lee, RPh, MS  
Regulatory Review Officer  
Division of Advertising and Promotion Review 1  
Office of Prescription Drug Promotion

{See appended electronic signature page}

Samuel M. Skariah, PharmD, RAC  
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<sup>7</sup> See FD&C Act sections 201(n), 502(a), 502(n).

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/s/  
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KOUNG U LEE  
09/08/2016

SAMUEL M SKARIAH  
09/08/2016