

Zelnorm

Single Patient IND Packet

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1. Zelnorm Background

Zelnorm (tegaserod maleate) is a 5-hydroxytryptamine 5-HT₄ receptor partial agonist that enhances intestinal motility and stimulates intestinal secretion. It is indicated for men and women with irritable bowel syndrome with constipation (IBS-C), and women under 55 with chronic idiopathic constipation (CIC).

In 2007, the Food and Drug Administration asked Novartis to suspend its United States marketing and sales voluntarily, because a safety analysis found a higher chance of heart attack, stroke, and unstable angina (heart/chest pain) in patients treated with Zelnorm, compared with treatment with an inactive substance (placebo). Marketing was voluntarily suspended in the United States. The decision was based on a study of more than 11,600 patients treated with Zelnorm and over 7,000 patients treated with the placebo (see Related Information below).

Today, FDA authorizes the restricted use of Zelnorm through expanded access under a Single Patient IND (SPI). US WorldMeds, LLC has agreed to continue to supply Zelnorm in these situations when no comparable or satisfactory alternative drug or therapy is available to the patient. The following conditions are cause for denial of authorization:

- prior history of heart attack or stroke
- unstable angina
- hypertension
- hyperlipidemia
- diabetes
- age greater than 55 years
- smoking
- obesity
- depression
- anxiety
- suicidal ideation

2. Application Process for Single Patient INDs

Physicians can obtain Zelnorm for a single patient by submitting a Single Patient IND application to the FDA (see 21 CFR 312.310¹). Single Patient INDs are made available under the FDA Expanded Access Program, and are processed according to the following steps which should occur in less than 30 days. Every effort will be made to meet a physician's request for expedited review. **It is imperative that you are available during our review of your application in the event that we have questions. Unresolved issues may lead to a clinical hold.**

Application Checklist for Zelnorm Single Patient IND

1. Cover letter (see Appendix A for template)
 2. FDA Form 3926 (see Appendix B for instructions²) All fields should be complete, including additional requests in red.
 3. Curriculum Vitae (CV)
 4. Copy of Informed Consent planned for use (see [Informed Consent Document](#) section).
- Please ensure each item is enclosed, otherwise the application will be considered incomplete. Only complete applications will be reviewed.**

Securing Zelnorm Shipment

USWorldMeds (the manufacturer of this unapproved drug) is willing to provide it to IND holders. Once we determine your IND is allowed to proceed, we will provide USWorldMeds with the IND number and your contact information in order for you to establish shipment arrangements. You may contact USWorldMeds directly to order Zelnorm:

USWM

Mallory Alonso, Manager, Medical Affairs

malonso@usworldmeds.com and RegulatoryAffairs@usworldmeds.com

502-815-8233

Contacting your IRB

An Institutional Review Board (IRB) means any board, committee, or other group formally designated by an institution to review, to approve the initiation of, and to conduct periodic review of biomedical research involving human subjects. The primary purpose of IRB review is to assure that the rights and welfare of human subjects are protected, including by determining that informed consent is obtained in accordance with and to the extent required by Federal requirements. Many institutions have their own IRB to oversee human subjects research conducted within the institution or by the staff of the institution. If the physician does not have access to a local IRB, an independent IRB may be used. The

¹To search Code of Federal Regulations (CFR) Title 21, visit:

<http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcr/CFRSearch.cfm>

² Note that FDA Forms 1571 and 1572 are still acceptable. See the following website for forms and instructions:

<http://www.fda.gov/AboutFDA/ReportsManualsForms/Forms/default.htm>

Department of Health & Human Services' Office for Human Research Protections maintains a database of registered IRBs. Go to <http://ohrp.cit.nih.gov/search/irbsearch.aspx?styp=bsc> and click on "Advanced Search." Enter your state to find registered IRBs in your area.

For questions about locating an IRB, you may contact the FDA for assistance (Human Subject Protection Branch: CDER-OSI-GCPReferrals@fda.hhs.gov, or contact Quynh-Van Tran at 301-796-0185).

Informed Consent Documents

Your IRB may have an Informed Consent Document that they prefer you use. When creating an Informed Consent, please consult the elements of informed consent:

<http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=50.25>

The informed consent document (ICD) should adequately address the potential risks associated with Zelnorm including a higher chance of heart attack, stroke, and unstable angina (heart/chest pain) in patients treated with Zelnorm, compared with treatment with an inactive substance (placebo).

Secure Email

Secure email between FDA and sponsors is useful for informal communications when confidential information may be included in the message (e.g., confidential patient information). Parties who would like to establish secure email with FDA should email a request to SecureEmail@fda.hhs.gov.

Follow-up Submissions

Form FDA 3926 may be used for original individual patient expanded access INDs and follow up submissions (e.g., withdrawal request, safety report, annual reports). Remember to check to appropriate box in item 3 to indicate the intent.

Appendix A – Cover Letter Template

[Date]

Dragos Roman, M.D.
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Gastroenterology and Inborn Errors Products
Central Document Room 5901-B Ammendale Rd.
Beltsville, Md. 20705-1266

Subject: New Single Patient IND Application for Zelnorm

Dear Dr. Roman,

I am hereby submitting an Investigational New Drug (IND) application under section 505(i) of the Federal Food, Drug, and Cosmetic Act and in accord with 21 CFR 312 for Zelnorm.

This application contains the following (*please check all that apply*):

- Form 3926 (all fields complete)
or completed Forms 1571 and 1572
- Copy of Informed Consent

I claim a categorical exclusion from environmental assessment requirements (under 21 CFR 25.31[e]) for this IND. To my knowledge, no extraordinary circumstances exist.

If my IND is allowed to proceed, I consent to allowing FDA to provide USWorldMeds with my information including my name and IND number.

Sincerely,

Appendix B – FDA Form 3926 and Instructions

Download and complete the form online before printing and signing:

<http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM504572.pdf>

The form below is for instructional purposes only. You may type directly into the online form. You can expand any field to fit pertinent information or may attach a separate sheet.

Please do not hand-write on the example form below.

Some instructions are overlaid in **red** below, and additional instructions can be found at:

<http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM504574.pdf>

DEPARTMENT OF HEALTH AND HUMAN SERVICES Food and Drug Administration		Form Approved: OMB No. 0910-0814 Expiration Date: April 30, 2019 See PRA Statement on last page.
Individual Patient Expanded Access Investigational New Drug Application (IND) <i>(Title 21, Code of Federal Regulations (CFR) Part 312)</i>		
1. Patient's Initials		2. Date of Submission (mm/dd/yyyy)
3.a. Initial Submission <input checked="" type="checkbox"/> Select this box if this form is an initial submission for an individual patient expanded access IND, and complete only fields 4 through 8, and fields 10 and 11.	3.b. Follow-Up Submission <input type="checkbox"/> Select this box if this form accompanies a follow-up submission to an existing individual patient expanded access IND, and complete the items to the right in this section, and fields 8 through 11.	Investigational Drug Name Physician's IND Number
4. Clinical Information		
Indication Proposed treatment use, e.g. irritable bowel syndrome with constipation (IBS-C) or chronic idiopathic constipation (CIC).		
Brief Clinical History (<i>Patient's age, gender, weight, allergies, diagnosis, prior therapy, response to prior therapy, reason for request, including an explanation of why the patient lacks other therapeutic options</i>) Include ROME III classification and whether there is any history of cardiovascular events or risk factors, depression or obesity. Include DOB.		
5. Treatment Information		
Investigational Drug Name Zelnorm		
Name of the entity that will supply the drug (<i>generally the manufacturer</i>) UsWorldMeds		
FDA Review Division (<i>if known</i>) Division of Gastroenterology and Inborn Errors Products (DGIEP)		
Treatment Plan (<i>Including the dose, route and schedule of administration, planned duration, and monitoring procedures. Also include modifications to the treatment plan in the event of toxicity.</i>) For patients <12 years old, include weight and/or dosage in mg/kg		
6. Letter of Authorization (LOA), if applicable (<i>generally obtained from the manufacturer of the drug</i>) <input type="checkbox"/> I have attached the LOA. (<i>Attach the LOA; if electronic, use normal PDF functions for file attachments.</i>) Note: If there is no LOA, consult the Form Instructions. N/A if using UsWorldMeds		
7. Physician's Qualification Statement (<i>Including medical school attended, year of graduation, medical specialty, state medical license number, current employment, and job title. Alternatively, attach the first few pages of physician's curriculum vitae (CV), provided they contain this information. If attaching the CV electronically, use normal PDF functions for file attachments.</i>)		

8. Physician Name, Address, and Contact Information

Physician Name (Sponsor)		Email Address of Physician
Address 1 (Street address, No P.O. boxes)		Email is essential to communication about your IND and is our primary method of contact.
Address 2 (Apartment, suite, unit, building, floor, etc.)		
City		Telephone Number of Physician
State		Facsimile (FAX) Number of Physician
ZIP Code		Physician's IND number, if known

9. Contents of Submission

This submission contains the following materials, which are attached to this form (select all that apply). If none of the following apply to the follow-up communications, use Form FDA 1571 for your submission.

- | | |
|---|--|
| <input type="checkbox"/> Initial Written IND Safety Report | <input type="checkbox"/> Change in Treatment Plan |
| <input type="checkbox"/> Follow-up to a Written IND Safety Report | <input type="checkbox"/> General Correspondence |
| <input type="checkbox"/> Annual Report | <input type="checkbox"/> Response to FDA Request for Information |
| <input type="checkbox"/> Summary of Expanded Access Use (treatment completed) | <input type="checkbox"/> Response to Clinical Hold |

10.a. Request for Authorization to Use Form FDA 3926

- I request authorization to submit this Form FDA 3926 to comply with FDA's requirements for an individual patient expanded access IND.

10.b. Request for Authorization to Use Alternative IRB Review Procedures

- I request authorization to obtain concurrence by the Institutional Review Board (IRB) chairperson or by a designated IRB member, before the treatment use begins, in order to comply with FDA's requirements for IRB review and approval. This concurrence would be in lieu of review and approval at a convened IRB meeting at which a majority of the members are present.

11. Certification Statement: I will not begin treatment until 30 days after FDA's receipt of a completed application and all required materials unless I receive earlier notification from FDA that treatment may begin. I also agree not to begin or continue clinical investigations covered by the IND if those studies are placed on clinical hold. I also certify that I will obtain informed consent, and that an Institutional Review Board (IRB) will be responsible for initial and continuing review and approval of this treatment use, consistent with applicable FDA requirements. I understand that in the case of an emergency request, treatment may begin without prior IRB approval, provided the IRB is notified of the emergency treatment within 5 working days of treatment. I agree to conduct the investigation in accordance with all other applicable regulatory requirements.

WARNING: A willfully false statement is a criminal offense (U.S.C. Title 18, Sec. 1001).

Signature of Physician	Date
To enable the signature field, please fill out all prior required fields. For a list of required fields which have not yet been filled out, please click here.	

For FDA Use Only		
Date of FDA Receipt	Is this an emergency individual patient IND? <input type="checkbox"/> Yes <input type="checkbox"/> No	Is this indication for a rare disease (prevalence < 200,000 in the U.S.)? <input type="checkbox"/> Yes <input type="checkbox"/> No
IND Number		

This section applies only to requirements of the Paperwork Reduction Act of 1995.

DO NOT SEND YOUR COMPLETED FORM TO THE PRA STAFF EMAIL ADDRESS BELOW.

The burden time for this collection of information is estimated to average 45 minutes per response, including the time to review instructions, search existing data sources, gather and maintain the data needed and complete and review the collection of information. Send comments regarding this burden estimate or any other aspect of this information collection, including suggestions for reducing this burden, to:

Department of Health and Human Services
Food and Drug Administration
Office of Operations
Paperwork Reduction Act (PRA) Staff
PRAStaff@fda.hhs.gov

"An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB number."