DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

TRANSMITTED BY FACSIMILE

Mark C. Roessel
Senior Director, Regulatory Affairs
Indevus Pharmaceuticals, Inc.
33 Hayden Avenue
Lexington, MA 02421

Re: NDA # 21-595
Sanctura® (trospium chloride) 20 mg Tablets
MACMIS ID #15930

Dear Mr. Roessel:

This letter notifies Indevus Pharmaceuticals, Inc. (Indevus), and by copy, Allergan, Inc., which co-promotes Sanctura® (trospium chloride) 20 mg Tablets (Sanctura) with Indevus[1], that the Division of Drug Marketing, Advertising, and Communications (DDMAC) of the U.S. Food and Drug Administration (FDA) has reviewed a professional journal advertisement ("Journal Ad") (SANC-0105-2) for Sanctura submitted by Indevus under cover of Form FDA-2253. The Journal Ad is false or misleading because it makes unsubstantiated superiority claims for the drug, omits and minimizes material risk information, and overstates the efficacy of Sanctura. Therefore, the Journal Ad misbrands Sanctura in violation of the Federal Food, Drug, and Cosmetic Act (the Act), 21 U.S.C. 352(n) & 321(n); and FDA implementing regulations. *See* 21 CFR 202.1(e)(3)(i); (e)(5)(i), (ii), (iii); (e)(6)(i), (ii); & (e)(7)(iii) and (viii).

Background

The Indications and Usage section of the FDA-approved product labeling for Sanctura (PI) states:

> Sanctura is indicated for the treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and urinary frequency.

Sanctura also is associated with numerous risks. The PI contains contraindications for use in patients with urinary retention, gastric retention, or uncontrolled narrow-angle glaucoma and in patients who are at risk for these conditions, as well as in patients who have demonstrated hypersensitivity to the drug or its ingredients. The PI also contains numerous precautions, including drug interactions with other anticholinergic agents and drugs eliminated by active tubular secretion. As stated in the PI, the most common adverse events associated with

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[1] At the date of dissemination of the Journal Ad, Esprit Pharma, Inc. (Esprit) co-promoted Sanctura with Indevus. In a news release dated September 19, 2007 (accessed from http://salesandmarketingnetwork.com/news_release_print.php?ID=2020564 on April 25, 2008), Allergan, Inc. (Allergan) announced that it had entered into an agreement with Esprit Pharma Holding Company, Inc. to acquire Esprit. In a news release dated October 17, 2007 (accessed from http://agn360.client.shareholder.com/releaseddetail.cfm?ReleaseID=269674 on March 10, 2008), Allergan announced the completion of this transaction.

Sanctura 20 mg twice daily relative to placebo were: dry mouth (20.1%, 5.8%); constipation (9.6%, 4.6%); and headache (4.2%, 2.0%).

Unsubstantiated Superiority Claims

The Journal Ad misleadingly suggests that Sanctura is superior to other drug therapies for overactive bladder (OAB), when this has not been demonstrated by substantial evidence or substantial clinical experience. For example, the Journal Ad includes the following claims, presented around an illustration of a large four-leaf clover surrounded by a golden halo, standing above numerous three-leaf clovers (emphasis original):

- **"In a world where many OAB drugs are the same...ONE stands out."**
- **"Look no further."**
- **"SANCTURA stands alone.**
  The unique quaternary structure makes all the difference.

  Dual-action mechanism

  Day 1 relief with sustained efficacy

  A safe choice, low CNS risk

  No known metabolic drug interactions

  Quality of life significantly improved"
  (footnotes omitted)

The totality of these claims and presentations misleadingly suggest that Sanctura confers more therapeutic benefits than other therapies for OAB, when this has not been demonstrated by substantial evidence or substantial clinical experience. Specifically, the presentation misleadingly suggests that Sanctura is superior to other OAB therapies based on its clinical pharmacology. While the intrinsic chemical structure (*i.e.*, quaternary amine) of Sanctura is different from other OAB drugs, FDA is not aware of any studies demonstrating that the structure of Sanctura offers any distinct patient benefits or conveys any clinically significant advantage, or any studies indicating that Sanctura is superior to other drugs for the treatment of OAB - we are unaware of any study comparing Sanctura with any other treatment for overactive bladder. If you have such studies, please submit them to FDA for review.

Omission and Minimization of Risk Information

Promotional materials are misleading if they fail to reveal material facts in light of the representations made by the materials or with respect to consequences that may result from the use of the drug as recommended or suggested by the materials. The Journal Ad makes numerous claims for Sanctura, including "No known metabolic drug interactions." (footnotes omitted) This claim is misleading because it presents positive information concerning drug-drug interactions, but omits material risk information associated with the concomitant use of Sanctura and other drugs. We acknowledge that metabolic drug interactions between

Sanctura and other medications are not expected.[2] However, as stated in the Precautions section of the PI, Sanctura is associated with risks related to drug interactions with other anticholinergic agents. In addition, the PI recommends "careful patient monitoring" for patients receiving Sanctura concomitantly with drugs eliminated by active tubular secretion (e.g., procainamide, pancuronium, morphine, vancomycin, metformin, and tenofovir). By presenting claims concerning the lack of metabolic drug interactions without disclosing the risks associated with the concomitant use of Sanctura with other anticholinergic agents, as well as the potential for pharmacokinetic interactions with drugs that are eliminated by active tubular secretion, the Journal Ad misleadingly suggests that Sanctura is safer than has been demonstrated by substantial evidence or substantial clinical experience. We note the inclusion of a bolded, boxed reference, "Please see accompanying Brief Summary of full Prescribing Information," at the bottom of one side of the piece; this statement, however, is not sufficient to provide appropriate qualification or pertinent information for the claims made in the piece. *See* 21 CFR 202.1(e)(3)(i).

The Journal Ad omits other important risk information as well. Although it contains information regarding Sanctura's contraindications, the ad fails to communicate pertinent risks such as the commonly experienced adverse events associated with Sanctura, i.e., dry mouth, constipation, and headache. By omitting important disclosures concerning risks associated with Sanctura, the Journal Ad misleadingly suggests that Sanctura is safer than has been demonstrated by substantial evidence or substantial clinical experience. The omission of these risks is exacerbated by the claim in the Ad that Sanctura is "A safe choice," which further minimizes the risks associated with the use of Sanctura.

We note that the problems above are magnified because the Journal Ad fails to present risk information with a prominence and readability reasonably comparable with the presentation of information relating to the effectiveness of Sanctura. Throughout the Journal Ad, effectiveness claims are presented using large, bolded, colorful text and graphics. In contrast, the risk information that is presented is relegated to the bottom of the first page of the Journal Ad and is presented in a single block paragraph in small, black font following a statement of the indication for use, without any signal to indicate to the reader that it is important risk information.

Overstatement of Efficacy

Promotional materials are misleading if they contain representations or suggestions that the drug is better or more effective than has been demonstrated by substantial evidence or substantial clinical experience. The Journal Ad claims, "Day 1 relief...." This time to onset of effect claim is misleading because it is not supported by substantial evidence or substantial clinical experience. The reference[3] cited for this claim is a post-hoc analysis of efficacy data from one of the clinical studies (described in the Clinical Studies section of the PI) in which patients with overactive bladder were randomized to placebo or Sanctura. The onset of action regarding urge urinary incontinence was analyzed using the reverse stepwise method,

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[2] According to the Pharmacokinetics and Drug-Drug Interactions sections of the Sanctura PI, *in vitro* studies suggest a lack of inhibition at clinically relevant concentrations of Sanctura on seven cytochrome P450 isoenzyme substrates (CYP1A2, 2A6, 2C9, 2C19, 2D6, 2E1, and 3A4), and no clinically relevant drug-drug interactions with the metabolism of Sanctura are expected.

[3] Delbert R, Cline K, Harris R, et al. Time to onset of improvement in symptoms of overactive bladder using antimuscarinic treatment. *BJU Intl* 2006;97:540-6.

i.e., changes at day 7 were compared, and if there was a significant difference between the Sanctura and the placebo groups ($P \leq 0.05$), then data for day 6 were tested, and so on. Although this approach could be acceptable if planned prospectively, the analysis of the data in this case was done retrospectively. This retrospective analysis does not soundly support the claim made. *See* 21 CFR 202.1(e)(7)(iii).

Furthermore, the time to onset claim in the Journal Ad is based on only one of two studies identified as "pivotal" that were submitted to the NDA. Although both studies were given equal weight in the clinical studies section of the PI, the reverse stepwise analysis was not performed on the other pivotal trial. The results from this other pivotal trial showed statistical significance compared to placebo on Day 7 and not on any day prior to then. This favorable day one claim is thus based on a selective presentation of the most favorable data, and is not supported by substantial evidence. For this reason, it is misleading.

The Journal Ad also claims, "**Quality of life significantly improved**" (footnote omitted). This claim is misleading because it implies that Sanctura significantly improves patients' quality of life, when this has not been demonstrated by substantial evidence or substantial clinical experience. In support of this claim, the Journal Ad references a study that is not adequately designed to substantiate the claim. Specifically, the instrument used to measure "quality of life" in the referenced study was the Incontinence Impact Questionnaire (IIQ), which measures the impact of overactive bladder on travel, physical activity, social relationships, and emotional health, but not on other domains covered by the broad claim of "quality of life", such as non-health-related aspects of life including work productivity and financial stability. Additionally, the referenced study did not show a significant improvement on <u>all</u> of the IIQ subscales; specifically, the results demonstrated that Sanctura did <u>not</u> affect the physical activity subscale that reflects the impact of incontinence on patient perception of overall physical health, shopping activities, and ability to perform household chores. Moreover, the IIQ used in this study was not validated in men, and the IIQ scores in men did not improve in this study. Therefore, this reference cannot support the claim in the Ad that Sanctura will significantly improve patients' quality of life.

Conclusion and Requested Action

For the reasons discussed above, the Journal Ad misbrands Sanctura in violation of the Act, 21 U.S.C. 352(n) & 321(n), and FDA implementing regulations. 21 CFR 202.1(e)(3)(i); (e)(5)(i), (ii), (iii); (e)(6)(i), (ii); & (e)(7)(iii) and (viii).

DDMAC requests that Indevus immediately cease the dissemination of violative promotional materials for Sanctura such as those described above. Please submit a written response to this letter on or before February 10, 2009, stating whether you intend to comply with this request, listing all promotional materials (with the 2253 submission date) in use for Sanctura and Sanctura XR (trospium chloride extended release capsules) as of the date of this letter, identifying which of these materials contain violations such as those described above, and explaining your plan for discontinuing use of such materials. Please direct your response to me at the Food and Drug Administration, Division of Drug Marketing, Advertising, and Communications, 5901-B Ammendale Road, Beltsville, MD 20705, facsimile at (301) 847-8444. In all future correspondence regarding this matter, please refer to MACMIS ID #15930

in addition to the NDA number. We remind you that only written communications are considered official.

The violations discussed in this letter do not necessarily constitute an exhaustive list. It is your responsibility to ensure that your promotional materials for Sanctura comply with each applicable requirement of the Act and FDA implementing regulations.

Sincerely,

{See appended electronic signature page}

Amy Toscano, Pharm.D., CPA
Regulatory Review Officer
Division of Drug Marketing,
Advertising, and Communications

cc: Bhavana Desai
Director
Allergan, Inc.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Amy Toscano
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