DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

TRANSMITTED BY FACSIMILE

NOV 1 2004

Kathleen Baum
Regulatory Affairs Coordinator
Mallinckrodt Inc.
675 McDonnell Boulevard
P.O. Box 5840
St. Louis, MO 63134

Re: ANDA # 75-983
Tramadol Hydrochloride Tablets, 50 mg
MACMIS # 12473

Dear Ms. Baum:

The Division of Drug Marketing, Advertising, and Communications (DDMAC) has reviewed a professional exhibit panel (MPBC011) for Tramadol Hydrochloride Tablets submitted by Mallinckrodt Inc. (Mallinckrodt) under cover of Form FDA 2253. The exhibit panel is false or misleading in violation of Sections 502(a) and 201(n) of the Federal Food, Drug, and Cosmetic Act (Act) (21 U.S.C. § 352(a)) because it omits risk information and claims that Tramadol is more effective than has been demonstrated by substantial evidence or substantial clinical experience

Background

According to the FDA-approved labeling (PI), Tramadol is a centrally acting synthetic opioid analgesic indicated for the management of moderate to moderately severe pain in adults.

The "Contraindications" section of the PI states:

> Tramadol should not be administered to patients who have previously demonstrated hypersensitivity to tramadol, any other component of this product or opioids. Tramadol is contraindicated in any situation where opioids are contraindicated, including acute intoxication with any of the following: alcohol, hypnotics, narcotics, centrally acting analgesics, opioids or psychotropic drugs. Tramadol may worsen central nervous system and respiratory depression in these patients.

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Furthermore, the "Warnings" section of the PI contains the following bolded warnings:

> **Seizure Risk**
> **Seizures have been reported in patients receiving tramadol within the recommended dosage range. Spontaneous post-marketing reports indicate that seizure risk is increased with doses of tramadol above the recommended range. Concomitant use of tramadol increases the seizure risk in patients taking:**
> - **Selective serotonin reuptake inhibitors (SSRI antidepressants or anorectics),**
> - **Tricyclic antidepressants (TCAs), and other tricyclic compounds (e.g., cyclobenzaprine, promethazine, etc.), or**
> - **Other opioids.**
>
> **Administration of tramadol may enhance the seizure risk in patients taking:**
> - **MAO inhibitors (see also WARNINGS - Use with MAO Inhibitors),**
> - **Neuroleptics, or**
> - **Other drugs that reduce the seizure threshold.**
>
> **Risk of convulsions may also increase in patients with epilepsy, those with a history of seizures, or in patients with a recognized risk for seizure (such as head trauma, metabolic disorders, alcohol and drug withdrawal, CNS infections). In tramadol overdose, naloxone administration may increase the risk of seizure.**

The PI lists other risk information associated with use of Tramadol, including, but not limited to, the following statement in the "Warning" section:

> **Physical Dependence and Abuse**
> Tramadol may induce psychic and physical dependence of the morphine-type (μ-opioid) (See DRUG ABUSE AND DEPENDENCE). Tramadol should not be used in opioid-dependent patients. Tramadol has been shown to reinitiate physical dependence in some patients that have been previously dependent on other opioids. Dependence and abuse, including drug-seeking behavior and taking illicit actions to obtain the drug, are not limited to those patients with prior history of opioid dependence.

Omission of Risk Information

The exhibit panel is misleading because it presents effectiveness claims for Tramadol but fails to reveal any risk information related to its use. We acknowledge that the exhibit panel includes the statement, "Full prescribing information available at this booth." However, this reference to the full prescribing information does not mitigate the complete omission of risk information in the exhibit panel. By failing to reveal any risk information, Mallinckrodt misleadingly suggests that Tramadol is safer than has been demonstrated by substantial evidence or substantial clinical experience. *Cf.* 21 CFR 202.1(e)(6)(i).

Overstatement of Efficacy

The exhibit panel presents the effectiveness claim, "for moderate to moderately severe pain." This claim is misleading, because it implies that the drug is effective in all patient

populations. We are not aware of substantial evidence or substantial clinical experience substantiating this claim. According to the PI, "Tramadol is indicated for the management of moderate to moderately severe pain **in adults**" (emphasis added). Your failure to disclose the complete indication in the exhibit panel is false or misleading because it implies that Tramadol has been shown to be safe and effective for use in the pediatric population when, to our knowledge, such a claim has not been demonstrated by substantial evidence or substantial clinical experience.

Conclusion and Requested Action

The exhibit panel makes claims for Tramadol, but fails to disclose any risk information and misleadingly suggests that Tramadol is more effective than has been shown by substantial evidence or substantial clinical experience. Accordingly, the exhibit panel misbrands Tramadol in violation of section 502(a) of the Act, 21 U.S.C. § 352(a).

DDMAC requests that Mallinckrodt immediately cease the dissemination of promotional materials for tramadol the same as or similar to those described above. Please submit a written response to this letter on or before November 15, 2004 describing your intent to comply with this request, listing all promotional materials for Tramadol the same as or similar to 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, HFD-42, Rm. 8B-45, 5600 Fishers Lane, Rockville, Maryland 20857, facsimile at 301-594-6771. In all future correspondence regarding this matter, please refer to MACMIS ID # 12473 in addition to the ANDA number. We remind you that only written communications are considered official. If you choose to revise your promotional materials, DDMAC is willing to assist you in assuring that your revised materials comply with applicable provisions of the Act by reviewing your revisions before you use them in promotion.

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

Sincerely,

/S/

Jiaryin Wang, Pharm.D.
LT, USPHS
Regulatory Review Officer
Division of Drug Marketing,
Advertising, and Communications