



TRANSMITTED BY FACSIMILE

Steven Hanley
President Imaging Division
Mallinckrodt Inc.
675 McDonnell Boulevard
P.O. Box 5840
Hazelwood, MO 63042

Re: ANDA 87-388
MD-GASTROVIEW® (Diatrizoate Meglumine and Diatrizoate Sodium Solution USP)
NDA 20-937
OptiMARK® (Gadoversetamide Injection)
MACMIS# 14453

WARNING LETTER

Dear Mr. Hanley:

The Division of Drug Marketing, Advertising, and Communications (DDMAC) has reviewed exhibit booth panels (panels) for MD-Gastroview (Diatrizoate Meglumine and Diatrizoate Sodium Solution USP) and OptiMARK (Gadoversetamide Injection) entitled, "Break Through to a Brighter View" and "The Power to Illuminate," respectively, submitted by Mallinckrodt Medical under cover of Form FDA 2253. The panels are misleading because they present effectiveness claims but fail to reveal any risk information related to the use of MD-Gastroview and OptiMARK. Thus, the exhibit booth panels misbrand the drugs in violation of the Federal Food, Drug, and Cosmetic Act (the Act), 21 U.S.C. §§ 352(a) and 321(n).

Background

MD-Gastroview (Diatrizoate Meglumine and Diatrizoate Sodium Solution USP)

As stated in the Indications and Usage section of the FDA-approved product labeling (PI):

MD-GASTROVIEW (Diatrizoate Meglumine and Diatrizoate Sodium Solution) is indicated for radiographic examination of segments of the gastrointestinal tract (esophagus, stomach, proximal small intestine, and colon). The preparation is particularly indicated when a more viscous agent such as barium sulfate, which is not water soluble, is not feasible or is potentially dangerous.

MD-GASTROVIEW may also be used as an adjunct to contrast enhancement in computed tomography of the torso (body imaging); the preparation is indicated, in conjunction with intravenous administration of a radiopaque contrast agent, when unenhanced imaging may not provide sufficient definition in distinguishing normal loops of bowel from adjacent organs or areas of suspected pathology.

Additionally, MD-Gastroview is associated with several risks including the following taken from the WARNINGS, PRECAUTION and ADVERSE REACTIONS sections of the PI (in pertinent part):

WARNINGS

A 1 in 4.6 (1:4.6) dilution of MD-GASTROVIEW yields an approximately isotonic 16.5 percent diatrizoate salts solution; less dilute solutions are hypertonic and may lead to intraluminal movement of fluid with resulting hypovolemia. In young or debilitated children and in elderly cachectic persons, the loss of plasma fluid may be sufficient to cause a shock-like state. . . . *Electrolyte disturbances must be corrected prior to using hypertonic solutions.* In debilitated patients and in patients with electrolyte imbalances, postprocedural monitoring of hydration, serum osmolarity, electrolytes and clinical status is essential. In pediatric or severely debilitated patients, the maintenance of an open intravenous fluid line for rehydration may be advisable should hypotension or shock supervene. [emphasis in original].

The possibility of accidental aspiration into the trachea or into a tracheoesophageal fistula following ingestion or instillation, could result in serious pulmonary complications (e.g., pulmonary edema or pneumonitis) even though the medium may be promptly expectorated.

PRECAUTIONS

General

The possibility of a reaction should always be considered. Patients at increased risk include those with a history of a previous reaction to a contrast medium, patients with a known sensitivity to iodine per se, and patients with a known clinical hypersensitivity (bronchial asthma, hay fever, and food allergies).

Rectal administration of undiluted MD-GASTROVIEW in any patient, particularly with large doses and/or in those with overdistention, has been reported to be associated with mucosal irritation.

Cases of hyperthyroidism have been reported with the use of oral contrast media. Some of these patients reportedly had multinodular goiters which may have been responsible for the increased hormone synthesis in response to excess iodine. Administration of an intravascular iodinated radiopaque diagnostic agent to a hyperthyroid patient precipitated thyroid storm; a similar situation could follow administration of oral preparations of iodides. Therefore, caution should be exercised when administering enteral gastrointestinal radiopaque agents to hyperthyroid and euthyroid goiterous patients.

Consideration should be given to the potential for precipitation of water-soluble contrast agents under conditions that may promote hyperacidity (i.e., fasting, emotional upset, or stress).

ADVERSE REACTIONS

Most adverse reactions to enteral diagnostic radiopaque agents are mild and transitory. Nausea, vomiting and/or diarrhea have occurred following ingestion of the contrast medium, particularly when high concentrations or large volumes of solution are administered.

OptiMARK (Gadoversetamide injection)

As stated in the Indications and Usage section of the FDA-approved PI:

CNS (Central Nervous System)

OptiMARK® Injection is indicated for use with magnetic resonance imaging (MRI) in patients with abnormal blood brain barrier or abnormal vascularity of the brain, spine and associated tissues.

Liver

OptiMARK® Injection is indicated for use with MRI to provide contrast enhancement and facilitate visualization of lesions with abnormal vascularity in the liver in patients who are highly suspect for liver structural abnormalities on computed tomography.

Additionally, OptiMARK is associated with several risks including the following taken from the WARNINGS, PRECAUTIONS, and ADVERSE REACTIONS sections of the PI (in pertinent part):

WARNINGS

Deoxygenated sickle erythrocytes have been shown in vitro studies to align perpendicular to a magnetic field; this may result in vaso-occlusive complications in vivo. The enhancement of magnetic moment by gadoversetamide may potentiate sickle erythrocyte alignment. OptiMARK® Injection in patients with sickle cell anemia and other hemoglobinopathies has not been studied....Patients with history of allergy, renal insufficiency or drug reaction should be observed for several hours after drug administration.

PRECAUTIONS

General

Some paramagnetic contrast agents may impair the visualization of existing lesions, which are seen on the unenhanced, noncontrast MRI. This may be due to effects of the paramagnetic contrast agent, imaging parameters, misregistration, etc. CAUTION SHOULD BE EXERCISED WHEN A CONTRAST ENHANCED INTERPRETATION IS MADE IN THE ABSENCE OF A COMPANION UNENHANCED MRI [emphasis in original].

Electrocardiographic Change

ECG parameters for the 0.1 mmol/kg dose were monitored in 93 subjects (6 volunteers and 87 patients) at multiple time points within the first day (immediate, 15, 30, 60 and 120 minutes and at 24 hours) of OptiMARK® Injection. Continuous ECG monitoring was not obtained. In these subjects, QT/QTc prolongations of $\geq 30 \leq 60$ msec and prolongations of ≥ 61 msec were noted in 15 and 3 subjects, respectively. None of these subjects had associated malignant arrhythmias. Similar QTc prolongations were noted in patients who received placebo and other doses of OptiMARK® Injection; however, the studies were not designed to establish causal relationships. The effects of dose, other drugs and other medical conditions were not studied. Caution should be exercised in patients who may be using medications or who may have underlying metabolic, cardiac, or other abnormalities that may predispose to cardiac arrhythmias.

Since gadoversetamide is cleared from the body by glomerular filtration, caution should be exercised in patients with impaired renal function.

The possibility of a reaction, including serious, life threatening, fatal, anaphylactoid or cardiovascular reactions or other idiosyncratic reactions should always be considered especially in those patients with a known clinical hypersensitivity, a history of asthma, or other respiratory disorders.

Repeat procedures: The safety of repeated doses has not been studied.

ADVERSE REACTIONS

The most commonly noted adverse events were headache (9.4%), vasodilatation (6.4%), taste perversion (6.2%), dizziness (3.7%), nausea (3.2%), and paresthesia (2.2%).

Omission of Important Risk Information

Promotional materials are misleading if they fail to reveal facts that are material in light of the representations made or with respect to consequences that may result from the use of the drug as recommended or suggested in the materials. These booth panels present several effectiveness claims for MD-Gastroview and OptiMARK, but they fail to include any of the risk information related to the use of these drugs.

For example, the MD-Gastroview booth panels include the claims:

- “Break Through to a Brighter View”
- “Market leader in oral iodinated contrast media”

And the OptiMARK booth panels include the claims:

- “The Power to Illuminate”
- “Excellent Image Quality”
- “Find What You’re Looking for With the Power of OptiMARK”

Despite these claims, the panels completely omit risk information, including the most frequently reported adverse experiences, precautions, and warnings from their respective PIs. In the case of the OptiMARK booth panel, the claim, “Excellent Safety Profile,” exacerbates this omission. By omitting this important information, the panels misleadingly suggest that MD-Gastroview and OptiMARK are safer than have been demonstrated by substantial evidence or substantial clinical experience. Cf. 21 C.F.R. §202.1(e). The statement, “See representative in booth for full prescribing information,” in small type at the lower left-hand corners of the panels does not mitigate this misleading presentation.

Conclusion and Requested Action

For the reasons discussed above, the panels misbrand MD-Gastroview and OptiMARK in violation of the Federal Food, Drug, and Cosmetic Act (the Act), 21 U.S.C. §§ 352(a) and 321(n).

Please note, DDMAC has made similar objections to your promotional material in Untitled Letters dated February 16, 2006, and November 1, 2004. On February 16, 2006, DDMAC issued an Untitled Letter¹ objecting to NeutroSpec™ [Kit for the Preparation of Technetium (99m Tc) fanolesomab] exhibit booth panels that, among other violations, omitted important risk information related to the use of NeutroSpec. In addition, DDMAC issued an Untitled Letter to Mallinckrodt on November 1, 2004, objecting to Tramadol Hydrochloride Tablets professional exhibit booth panels that, among other violations, omitted all risk information related to the use of Tramadol. As outlined in this letter, the “Break Through to a Brighter View” and “The Power to Illuminate” panels for MD-Gastroview and OptiMARK contain almost identical violations. DDMAC recommends that you review and correct promotional materials for products marketed by Mallinckrodt with similar violations.

DDMAC requests that Mallinckrodt immediately cease the dissemination of violative promotional materials for both MD-Gastroview and OptiMARK such as those described above. Please submit a written response to this letter on or before October 27, 2006, stating whether you intend to comply with this request, listing all violative promotional materials for both MD-Gastroview and OptiMARK such as those described above, and explaining your plan for discontinuing use of such materials. Because the violations described above are serious, we request, further, that your submission include a comprehensive plan of action to disseminate truthful, non-misleading, and complete corrective messages about the issues discussed in this letter to the audience(s) that received the violative promotional materials. Please direct your response to me at the Food and Drug Administration, Center for Drug Evaluation and Research, Division of Drug Marketing, Advertising, and Communications, 5901-B Ammendale Road, Beltsville, MD 20705-1266 or via facsimile at 301-796- 9878. In all future correspondence regarding this matter, please refer to MACMIS ID # 14453 in addition to the ANDA and NDA numbers. We remind you that only written communications are considered official.

¹ The letter was issued to Palatin Technologies Inc., and by copy, Mallinckrodt, which marketed NeutroSpec on behalf of Palatin.

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

Failure to correct the violations discussed above may result in FDA regulatory action, including seizure or injunction, without further notice.

Sincerely,

{See appended electronic signature page}

Thomas Abrams, R.Ph., M.B.A.
Director
Division of Drug Marketing,
Advertising, and Communications

**This is a representation of an electronic record that was signed electronically and
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/s/

Thomas Abrams
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