Dear Ms. Benson:

As part of its monitoring and surveillance program, the Division of Drug Marketing, Advertising, and Communications (DDMAC) of the U.S. Food and Drug Administration (FDA) has reviewed Bracco Diagnostics Inc.’s (Bracco) website at http://www.impactcin.com (IMPACT website) for its drug product, Isovue® (iopamidol injection) (Isovue).¹ The website contains false and unsubstantiated claims related to Isovue, and omits and minimizes the risks associated with the drug product. Thus, the website misbrands the drug in violation of the Federal Food, Drug, and Cosmetic Act (the Act), 21 U.S.C. 352(a) & (n); 321(n). Cf. 21 CFR 202.1(e)(3)(i); (e)(5); (e)(6)(i), (xviii); (e)(7)(i), (ii), (iii) & (viii).

Background

According to its FDA-approved product labeling (PI), Isovue is indicated for the following (in pertinent part):

ISOVUE (Iopamidol Injection) is indicated for angiography throughout the cardiovascular system, including cerebral and peripheral arteriography, coronary arteriography and ventriculography, pediatric angiocardiology, selective visceral arteriography and aortography, peripheral venography (phlebography), and adult and pediatric intravenous excretory urography and intravenous adult and pediatric contrast enhancement of computed tomographic (CECT) head and body imaging. . . .

Isovue has a boxed warning that states, “NOT FOR INTRATHECAL USE” (emphasis in original), which is further emphasized and elaborated on in the following bolded warning in the Warnings section of the PI (emphasis in original):

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¹ IMPACT website, at http://www.impactcin.com (last accessed January 7, 2010).
WARNINGS
Severe Adverse Events - Inadvertent Intrathecal Administration
Serious adverse reactions have been reported due to the inadvertent intrathecal administration of iodinated contrast media that are not indicated for intrathecal use.
These serious adverse reactions include: death, convulsions, cerebral hemorrhage, coma, paralysis, arachnoiditis, acute renal failure, cardiac arrest, seizures, rhabdomyolysis, hyperthermia, and brain edema. Special attention must be given to insure that this drug product is not inadvertently administered intrathecally.

Isovue is associated with other serious risks. The PI includes warnings regarding inhibition of blood coagulation; serious, rarely fatal, thromboembolic events; use in patients with severely impaired renal function; use in patients with multiple myeloma or other paraproteinemia, particularly in those with therapeutically resistant anuria; promotion of sickling in individuals who are homozygous for sickle cell disease; use in patients with known or suspected pheochromocytoma; and reports of thyroid storm following the use of iodinated radiopaque diagnostic agents in patients with hyperthyroidism or with an autonomously functioning thyroid nodule.

Additionally, the PI contains numerous precautions, including caution in hydrating patients with underlying conditions that may be worsened by fluid overload; predisposition of diabetic nephropathy to acute renal impairment which may precipitate lactic acidosis in patients taking biguanides; aggravation of the symptoms of myasthenia gravis; dangers of preparatory dehydration which may contribute to acute renal failure in patients with advanced vascular disease, diabetic patients, and in susceptible nondiabetic patients (often elderly with preexisting renal disease); serious, life-threatening, fatal, anaphylactoid or cardiovascular reactions, and potential transitory increase in the circulatory osmotic load in patients with congestive heart failure.

False Claims/Unsubstantiated Claims

There are numerous false claims and presentations on several webpages within the IMPACT website and in the video that describe the design of the IMPACT study. For example, the “Study Summary” webpage (http://www.impactcin.com/page3.htm) presents the following claims (bolded emphasis in original):

- “A prospective, head-to-head clinical study of Isovue® and Visipaque™ in patients at risk for CIN [contrast-induced nephropathy] undergoing contrast enhanced CT.”
- “…the largest, prospective, randomized, double-blind comparison of Visipaque with a nonionic monomer….”

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The “Study Design” webpage (http://www.impactcin.com/) presents the following claims (bolded emphasis in original; underlined emphasis added):

**Objective**
The aim of the IMPACT…study was to prospectively compare the incidence of contrast-induced nephropathy (CIN) following intravenous (IV) administration of equal doses of iopamidol-370 and iodixanol 320.

**Study Design**
A double-blind prospective, randomized, multicenter, parallel-group clinical trial in an at-risk patient population, to compare the renal tolerability of iopamidol-370 and iodixanol 320 in a common clinical setting.

**Methods:**
. . . .

CIN was the primary endpoint, defined as an absolute increase ≥0.5 mg/dL.

The video on the “IMPACT Video” webpage (http://www.impactcin.com/videoIMPACT.htm) presents the following claims accompanied by dramatic audio and visual elements (emphasis added):

- “Important news has emerged from this **clinically rigorous study.**”
- “The objective of this study was to **prospectively** compare the effects on renal function of iopamidol-370 and iodixanol-320 in patients with pre-existing moderate-to-severe renal impairment undergoing contrast-enhanced multi-detector CT.”
- “This was a multicenter, randomized, double-blinded, clinical trial with parallel-group study which enrolled 166 patients.”
- “What that means is that the medical community now has clinical head-to-head data to facilitate an informed decision on CIN.”
- “IMPACT was ’**rigorously controlled.**’”
- “Closest we have to the **truth** in the data available today.”

These claims and presentations falsely indicate that the IMPACT study was a prospective study that compared the primary endpoint of incidence of CIN between Isovue (iopamidol-370) and Visipaque (iodixanol-320). Contrary to these claims, the IMPACT study was **not** such a study, but rather was a post-hoc combination of two already-completed trials, INVICTA and VIRPACT, that were designed to study image quality as a primary endpoint and that listed CIN risk as a secondary endpoint. We are concerned about your false characterization of the IMPACT study design, as well as the misleading implication in your promotional materials that IMPACT, due to its touted design characteristics, provides “the truth” regarding the comparative incidence of CIN associated with Isovue versus Visipaque.

In addition to falsely characterizing the design of the IMPACT study, these promotional materials also present numerous comparative claims based on IMPACT. For example, the “Study Conclusions” webpage (http://www.impactcin.com/page2.htm) of the IMPACT website presents the following claims (bolded emphasis in original; underlined emphasis added):
Results

- There is no statistically significant difference in the rate of CIN between Isovue and Visipaque.

Conclusions

- The rate of CIN was similarly low in at-risk patients after IV administration of iopamidol-370 or iodixanol 320 for contrast-enhanced MDCT [multidetector computerized tomography].

Beneath the claims there are three graphical presentations comparing patients with SCr (serum creatinine) > 1.5 mg/dL or >2.0 mg/dL who were treated with Isovue-370 or Visipaque 320. The graphs present the results in terms of the CIN rate by absolute increase in SCr (percent of patients with increase in SCr ≥0.5 mg/dL) and percent increase in SCr (percent of patients with increase in SCr >25%). All three graphs display Isovue as numerically superior to Visipaque in terms of its impact on CIN rate. This webpage also contains the following statement (bolded emphasis in original; underlined emphasis added):

The results of this trial failed to demonstrate any difference in the incidence of CIN between equi-iodine doses of the nonionic dimer iodixanol 320, isotonic to human plasma, and the nonionic monomer iopamidol-370, hyperosmolar to human plasma, for intravenous use in patients with pre-existing stable chronically reduced kidney function.¹

The video on the “IMPACT Video” webpage (http://www.impactcin.com/videoIMPACT.htm) includes the following presentations (emphasis added):

- “The reality is IMPACT demonstrated no statistically significant difference in the rate of CIN between Isovue and Visipaque.”
- “Radiologists and nephrologists are looking for the best possible image and the greatest level of safety. That’s why this [IMPACT] study is so helpful.” This statement is presented in conjunction with a graphic presentation showing a 0% increase in CIN Rate for Isovue (by Absolute Increase in SCr) compared to a 28.6% increase for Visipaque, and is followed by a screen with the following textual presentation:
  - “iopamidol-370
    True choice for all your patients”

The “Study Summary” webpage (http://www.impactcin.com/page3.htm) presents the following claims (bolded emphasis in original; underlined emphasis added):

- “IMPACT study shows low rate of CIN with Isovue® and Visipaque™ following IV administration in at-risk patients.”²
- “Visipaque® did not demonstrate a statistically significant difference in the rate of CIN when compared to Isovue.”²
- “The results of this trial . . . , the largest, prospective, randomized, double-blind comparison of Visipaque with a nonionic monomer, failed to demonstrate any difference in the incidence of CIN . . . .”²
The above claims and presentations suggest that IMPACT has definitively proven that there is no statistically significant difference in the rate of CIN between Isovue and Visipaque, and that Isovue is in fact numerically superior to Visipaque in its impact on CIN rate and provides the “best possible image and greatest level of safety” compared to Visipaque. However, the IMPACT study does not constitute substantial evidence or substantial clinical experience to support the comparative claims and presentations referred to above. As stated above, the IMPACT study was a post-hoc combination of two already-completed trials. When looking for differences between treatment groups, a study must be designed prospectively to look for a well-specified difference, have a clear hypothesis, and an orderly method for testing the hypothesis. The design of the IMPACT study does not meet these requirements. Furthermore, the authors of the IMPACT study commented that, given the low incidence of CIN observed in the trial, “a study of about 3800 cases would be required to detect even a 50% reduction in the incidence of CIN with one contrast medium over the other.”

IMPACT examined a total of 166 patients.

Furthermore, the implied claim that Isovue provides “the best possible image and the greatest level of safety” compared to Visipaque is concerning because not only does it greatly minimize the serious risks associated with the drug product (see Background section above), but it also misleadingly implies that the IMPACT study provided substantial evidence that Isovue provides “the best possible image” compared with Visipaque. The IMPACT study was not designed to evaluate imaging quality as an endpoint.

**Omission and Minimization of Risk Information**

Promotional materials are misleading if they fail to reveal facts that are material 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 website presents numerous safety claims and presentations for Isovue, but omits the drug’s boxed warning regarding intrathecal administration and important accompanying information from the bolded warning regarding inadvertent intrathecal administration, in addition to other important risk information discussed in the Background section above. The only risk information included on the website are general statements concerning the risks of blood coagulation, thromboembolic events, and the possibility of severe reactions; important information from the PI regarding, for example, the risks of Isovue in certain patient populations, and the potential for serious, life-threatening, fatal anaphylactoid or cardiovascular reactions are not disclosed. As such, the overall effect of these presentations minimizes the risks associated with Isovue and misleadingly suggests that Isovue is safer than has been demonstrated. We note the statement, “Please click on the ‘downloads & PI’ tab for full prescribing information” at the lower left-hand corner of each webpage (similar language is presented at the end of the video on the “IMPACT Video” webpage); however, this statement does not mitigate the misleading omission of the risks associated with Isovue.

Moreover, the above referenced webpages, in addition to the “Study Design” webpage, minimize the risks associated with Isovue because they fail to present this information with comparable prominence to the presentations about the safety advantage of Isovue. Specifically, the “Study Conclusions,” “Study Summary,” and “Study Design” webpages use large headers and graphics centrally located on the pages to highlight a safety benefit of the drug - the reportedly low CIN risk of Isovue in the IMPACT study. In contrast to these
presentations, the disclosure of risk information is presented without headers, in a smaller font size, and without any signal to the reader that this is important risk information. Furthermore, the video on the “IMPACT Video” webpage uses superimposed text, voiceovers, and graphics and other pictorial representations to present the advantages of Isovue, while the risk information is relegated to the end of the video in a telescript format, with rapidly scrolling small text in single-spaced paragraph format, and with a voiceover that is spoken in a noticeably faster pace than in the efficacy presentations.

The overall effect of these misleading claims and presentations undermines the communication of important risk information, thereby minimizing the risks associated with Isovue and misleadingly suggesting that Isovue is safer than has been demonstrated.

**Conclusion and Requested Action**

For the reasons discussed above, the IMPACT website misbrands Isovue in violation of the Act, 21 U.S.C. 352(a) & (n); 321(n). Cf. 21 CFR 202.1(e)(3)(i); (e)(5); (e)(6)(i), (xviii); (e)(7)(i), (ii), (iii) & (viii).

DDMAC requests that Bracco immediately cease the dissemination of violative promotional materials for Isovue, such as those described above. Please submit a written response to this letter on or before January 22, 2010 stating whether you intend to comply with this request, listing all promotional materials (with the 2253 submission date) for Isovue that contain violations such as those described above, and explaining your plan for discontinuing use of such violative 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, facsimile at 301-847-8444. In all future correspondence regarding this matter, please refer to MACMIS #18021 in addition to the NDA numbers. 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 Isovue comply with each applicable requirement of the Act and FDA implementing regulations.

Sincerely,

{See appended electronic signature page}

Michelle Safarik, MSPAS, PA-C
Regulatory Review Officer
Division of Drug Marketing, Advertising, and Communications
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/s/

MICHELLE L SAFARIK
01/07/2010