



Dear Valued Customer:

The purpose of this communication is to provide you with clarification regarding the compliant multi-patient use of Isovue[®] (Iopamidol Injection) as provided in its multi-dose container: the Imaging Bulk Package (IBP).

The IBP is an **Isovue presentation** approved by the Food and Drug Administration (FDA) **for multi-patient use in the computed tomography (CT) suite**. The definition of the IBP is published in the United States Pharmacopeia (USP) Chapter <659> Packaging and Storage Requirements¹.

Since its introduction, there has been some confusion regarding the safe and compliant use of the IBP, and differences between the IBP and the Pharmacy Bulk Package (PBP). This communication will provide insight into the development of the IBP, the safe and compliant use of the IBP, and how the IBP supports full compliance with the regulations and requirements of accrediting agencies such as The Joint Commission (TJC).

Development of the IBP

Multiple-dose or multidose presentations are packaging systems that allow withdrawal of successive portions of a medication for parenteral administration to multiple patients without changing the safety, strength, quality, or purity of the remaining portion. The USP has traditionally defined two types of sterile multi-dose presentations for parenteral use: the multiple-dose container, which has a volume limit of 30 mL, and the PBP, which is exempt from the multiple-dose container volume limit. PBP contents are intended for use in pharmacy admixture programs, that is, the preparation of sterile admixtures of two or more drugs into a container of fluid for parenteral administration or through a sterile transfer device for the filling of empty sterile syringes.

In the 1990s, manufacturers of contrast media applied to the FDA for approval of multi-dose presentations of their radiographic iodinated contrast agents for intravascular use. Because the size of multi-dose presentations was always 200 mL or greater, the FDA defined these new containers as PBPs and requested that preparation of individual patient doses only be made in aseptic clean-air compounding areas, which are not typically available in standard radiology suites.

¹ United States Pharmacopeia: USP 40 – NF 35, Physical Tests, <659> Packaging and Storage Requirements, pages 529-534, Released November 1, 2016 / Official May 1, 2017.



In view of the important limitations of PBP use in radiology, Bracco worked closely with the FDA to define the regulatory pathway and validation requirements for the development of a new multi-dose, multi-patient Isovue presentation conducive to its safe use directly in standard Radiology or CT suites in conjunction with any marketed CT injector system.

The FDA approval of the Isovue[®] IBP was based on review of an innovative and extensive battery of testing that Bracco designed, with FDA concurrence, to prove the safety and integrity of the Isovue[®] IBP in resisting microbial contamination and maintaining the chemical stability of Isovue, when used with a specific transfer set, the Bracco Injengineering Transfer Set, to fill syringes on CT power injectors.

The development of the new IBP for use with the transfer set is described in detail in the publication: Spinazzi A, et al. Development of a New Imaging Bulk Package for Multi-patient Use in MDCT. AJR Am J Roentgenol 2015; 205: 697-702 (reprint attached).

As a result of the development program of the IBP and the approval by the FDA, the USP added the definition of the IBP as an injection packaging system, specifically intended for use in the Radiology or CT suite to deliver multiple single doses of contrast to multiple patients¹.

Differences between IBP and PBP

The IBP package is different and separate from any other multidose packaging system. In particular, when compared to the PBP:

- The IBP is a new packaging type specifically for use in any standard Radiology or CT suite to deliver multiple single doses of contrast to multiple patients. The IBP can be used in conjunction with a specific transfer set and any syringe-based contrast injection system on the US market (e.g., Medrad[®] Stellant[®] CT Injections System, or the Empower CTA[®] Contrast Injection System), or multipatient contrast management system specifically approved or cleared for use with the contrast agent provided in the IBP (e.g., the syringeless system: CT Exprès). The safe use of the IBP in this manner has been validated by an extensive battery of laboratory testing.
- The PBP is to be used only in an appropriate aseptic environment for sterile compounding, such as a pharmacy setting, with engineering controls, such as a laminar airflow hood or equivalent. A standard CT or Radiology suite or workroom typically does not meet these criteria and is not considered a suitable work area for PBPs. Also, no CT injector in the US market, syringe-based or syringeless, is approved for use with any PBP. Therefore, the use of the PBP in the Radiology or CT suite to withdraw doses and fill syringes on automated contrast injectors or in combination with syringeless multi-patient injection systems is contrary to the prescribing information approved by the FDA for both PBPs and injectors.



	Imaging Bulk Package (IBP)	Pharmacy Bulk Package (PBP)
Withdrawal of individual patient doses in any standard Radiology or CT suite	YES [in conjunction with the use of a specific transfer set]	NO [individual doses have to be withdrawn from the PBP and prepared within an appropriate aseptic environment for sterile compounding, such as a pharmacy setting]
Use in conjunction with CT injectors	YES	NO

Safe use of the IBP

Sterility may still remain a concern in Radiology if the Isovue IBP is not used as described in the package insert:

- The Isovue IBP is to be used only in a room designated for radiological procedures that involve intravascular administration of a contrast agent;
- The transferring of Isovue from the IBP should be performed utilizing aseptic technique;
- Prior to penetrating the container closure, the face of the container stopper should be swabbed with 70% isopropyl alcohol;
- The container closure may be penetrated only one time with a suitable sterile component of the automated contrast injection system or contrast management system approved or cleared for use with the IBP;
- Once the Isovue IBP is punctured, it should not be removed from the work area during the entire period of use, and the bottle should be maintained in an inverted position such that container contents are in continuous contact with the dispensing set;
- A maximum use time of 10 hours from initial closure entry is permitted to complete fluid transfer. Any unused Isovue must be discarded **10 hours after initial puncture of the IBP**;
- After the container closure is punctured, if the integrity of the IBP and the delivery system cannot be assured through direct continuous supervision, the IBP and all associated disposables for the automated contrast injection system or contrast management system should be discarded.

Bracco was very pleased to have had the opportunity to present information on the IBP, including the rigorous testing validating its safe use, to representatives from TJC in December of 2014 and again in November of 2015. Bracco has also presented the development and validation of the IBP to representatives of the Institute for Safe Medication Practice.



Conclusions

In summary, the Isovue[®] IBP is a new, fully compliant solution for use in the Radiology or CT suite to deliver multiple single doses of contrast agent to multiple patients undergoing contrast-enhanced CT examinations.

The IBP is a combination product which is to be used only with an automated contrast injection system or contrast management system approved or cleared for use with the contrast agent in the IBP. These include the Bracco Injengineering Transfer Set to fill sterile, single-use-only syringes on power injectors such as the Empower CTA[®]. **The safe use of the Isovue[®] IBP in this manner has been rigorously validated** and these data were submitted to FDA in Supplemental New Drug Applications and Premarket Notification Submissions [510(k)], which were subsequently approved / cleared by the Agency in June of 2014.

The link to the full to the Isovue[®] IBP full prescribing information (PI) can be accessed at: <http://imaging.bracco.com/us-en/products-and-solutions/x-ray-computed-tomography/isovue/prescribing-information>.

If you need additional information to support your use of the Isovue[®] IBP, either internally or with accrediting agencies, please do not hesitate to contact us at 800-257-5181, option 2, or at services.professional@diag.bracco.com.



LIFE FROM INSIDE

Attachment: Spinazzi A, et al. Development of a New Imaging Bulk Package for Multipatient Use in MDCT. AJR Am J Roentgenol 2015; 205: 697-702

Please see Important Safety Information below :

Isovue-300, 370 Imaging Bulk Package

Isovue (Iopamidol Injection) Imaging Bulk Package (IBP) is indicated for intravenous contrast enhancement of computed tomographic (CECT) imaging of the head and body in adult and pediatric patients.

Indications and Usage for Isovue in CT Procedures (Imaging Bulk Package):

IMPORTANT SAFETY INFORMATION:

Isovue IS NOT FOR INTRATHECAL USE. Iopamidol Injection is available as Isovue-M[®] for intrathecal administration.

Caution must be exercised in patients with severely impaired renal function, those with combined renal and hepatic disease, or anuria, particularly when larger and repeat doses are administered. Radiopaque diagnostic contrast agents are potentially hazardous in patients with multiple myeloma or other paraproteinemia, particularly in those with therapeutically resistant anuria. Caution should be exercised in hydrating patients with underlying conditions that may be worsened by fluid overload, such as congestive heart failure. Diabetic nephropathy may predispose to acute renal impairment following intravascular contrast media administration. Acute renal impairment following contrast media administration may precipitate lactic acidosis in patients who are taking biguanides. Preparatory dehydration is dangerous and 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). Patients should be well hydrated prior to and following iopamidol administration.

The possibility of a reaction, including serious, life-threatening, fatal, anaphylactoid or cardiovascular reactions, 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).

*The Isovue Imaging Bulk Package is for use with an automated contrast injector or a contrast management system approved or cleared for use with it.

Please see full Prescribing Information.

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch or call 1-800-FDA-1088.

Manufacturing Statement (to be used for all Isovue products):

Isovue and Isovue-M are currently manufactured for **Bracco Diagnostics Inc. at two locations:** BIPSO GmbH, Singen (Germany) and Patheon Italia S.p.A., Ferentino (Italy).

Trademark Notice:

Isovue and Isovue-M are registered trademarks of **Bracco Diagnostics Inc.**