October 2022, 10th

Subject: Temporary importation of non-FDA approved Zanosar® (Streptozocin powder for concentrate for solution for infusion) to address shortage

Dear Healthcare Professional,

Due to a critical shortage of Zanosar® 1g (streptozocin sterile powder) in the United States, Esteve Pharmaceuticals S.A.S (Esteve), in coordination with the U.S. Food and Drug Administration (FDA) intends to temporarily import non-FDA-approved Zanosar® (Streptozocin powder for concentrate for solution for infusion, dosage of 1g for single-use per vial) for U.S. patient use. Imported non-FDA approved Zanosar® (Streptozocin powder for concentrate for solution for infusion) is labeled in English and currently marketed in the European Union and United Kingdom. **It is important to note that although both the FDA-approved product and Esteve product share the same brand name Zanosar®, they are different as noted in the below comparison table.**

Dosage schedules requirements for the imported, non-FDA-approved Zanosar® (Streptozocin powder for concentrate for solution for infusion), are the same as the FDA-approved Zanosar® (streptozocin sterile powder). **In this regard, please keep referring to the FDA-approved package insert for dosage information.**

Storage requirement for the imported, non-FDA-approved Zanosar® (Streptozocin powder for concentrate for solution for infusion) is 2°C to 8°C in a refrigerator.

Zanosar's® therapeutic indication is the same in the European and FDA-approved products (treatment of patients with advanced pancreatic carcinoma), however the wording is different.

Table of Important Differences Between FDA-approved Zanosar and unapproved imported product		
	U.S Product	**Imported Product**
Pharmaceutical form	Sterile powder	Powder for concentrate for solution for infusion
Marketing Authorization number	NDC 00703-4636-01	PL 40308/0001

Esteve Pharmaceuticals SAS
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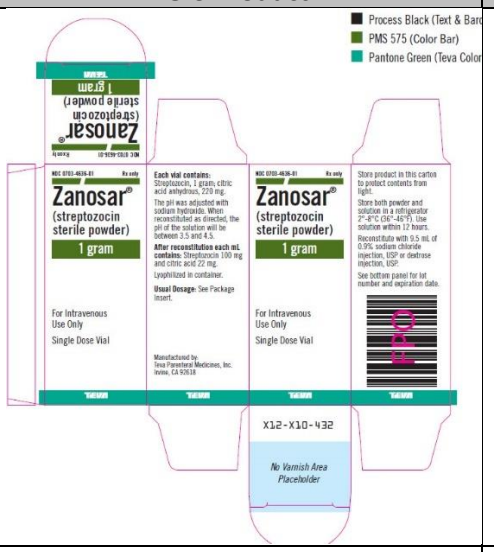
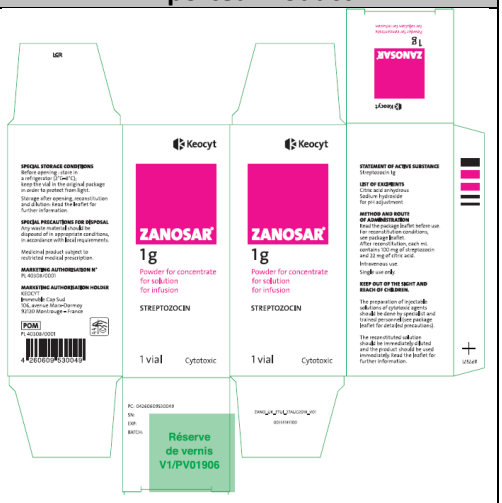
S.A.S au capital de 1 512 720 euros R.C.S. Nanterre 492 846 357

Table of Important Differences Between FDA-approved Zanosar and unapproved imported product		
	U.S Product	**Imported Product**
Container label		
Shelf life	18 months	36 months
Indication	Zanosar is indicated in the treatment of metastatic islet cell carcinoma of the pancreas. Responses have been obtained with both functional and nonfunctional carcinomas. Because of its inherent renal toxicity, therapy with this drug should be limited to patients with symptomatic or progressive metastatic disease.	Zanosar is indicated for the systemic treatment of adult patients with inoperable, advanced or metastatic, progressive and/or symptomatic, well-differentiated, G1 or G2 neuroendocrine tumours of pancreatic origin, in combination with 5-Fluorouracil.
Administration	ZANOSAR sterile powder should be administered intravenously by rapid injection or short/prolonged infusion. It is not active orally. Although it has been administered intraarterially, this is not recommended pending further evaluation of the possibility that adverse renal effects may be evoked more rapidly by this route of administration.	Zanosar should be administered intravenously by infusion. The duration of infusion should be between 30 minutes and 4 hours. The administration of Zanosar requires hyperhydration. This medicinal product is vesicant in nature and as such should be administered with caution through a free-flowing line. In case of extravasation, administration should be stopped immediately. Healthcare professionals should take appropriate protection measures. The initial aim is to minimize the volume of extravasated product into the surrounding tissues and to aspirate as much as possible product from the canula with a syringe. Cold packs should be applied and appropriate medical monitoring should be performed.

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	U.S Product	**Imported Product**
Instruction for reconstitution	Reconstitute ZANOSAR with 9.5 mL of dextrose injection, USP, or 0.9% sodium chloride injection, USP. The resulting pale-gold solution will contain 100 mg of streptozocin and 22 mg of citric acid per mL.	Each 20 mL vial of Zanosar must be reconstituted with 9.5 mL of sodium chloride 9 mg/ml (0.9%) solution for injection.
Reconstituted solution storage conditions	The total storage time for streptozocin after it has been placed in solution should not exceed 12 hours	The reconstituted solution should be immediately diluted. The chemical and physical in-use stability of the resulting solution has been demonstrated for 24 hours below 25°C in polyethylene Ecoflac® type bag containing a sodium chloride 9 mg/ml (0.9%) solution for injection.

Other Differences:

The barcode on the imported product label may not register accurately on U.S. scanning systems. Institutions should manually input the imported product information into their systems and confirm that the barcode, if scanned, provides correct information. Alternative procedures should be followed to assure that the correct drug product is being used and administered to individual patients.

In addition, the packaging of the imported product does not include serialization information. Esteve Zanosar® (Streptozocin powder for concentrate for solution for infusion) does not meet the Drug Supply Chain Security Act (DSCSA) requirements for the Interoperable Exchange of Information for Tracing of Human, Finished Prescription Drugs.

For your information, on the packaging (sticker, carton and leaflet), Keocyt is mentioned as the Marketing Authorization Holder instead of Esteve Pharmaceuticals S.A.S. Indeed, on January 17, 2022, the name change of the pharmaceutical company Keocyt has been amended to Esteve Pharmaceuticals S.A.S.

If you have any questions about the information contained in this letter, please contact us at:

ESTEVE medical inquiries department at contact-france@esteve.com.

Any quality problems or claims may be reported also by email to contact-france@esteve.com.

Any adverse events or any event related to safety associated with the use of non-FDA approved Zanosar® (Streptozocin powder for concentrate for solution for infusion) should be reported by email to safety@esteve.com.

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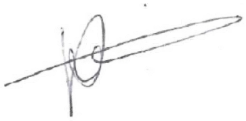
Adverse events or quality problems experienced with the use of this product may also be reported to the FDA's MedWatch Adverse Event Reporting Program either online, by regular mail, or by fax:

- Complete and submit the report Online: www.fda.gov/medwatch/report.htm
- Regular mail or Fax: Download form www.fda.gov/MedWatch/getforms.htm or call 1-800-332-1088 to request a reporting form, then complete and return to the address on the preaddressed form or submit by fax to 1-800-FDA-0178.

Yours faithfully,

Signature of authorized person:



Eugénie KOUBBI

Chief Pharmaceuticals Officer/ EUQPPV

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