October 2020

Direct Healthcare Professional Communication

TRISENOX (arsenic trioxide) – Risk of medication errors due to the introduction of 2 mg/ml concentration:
<u>New concentration:</u> 2 mg/ml vial to replace current approved 1 mg/ml glass ampoule of TRISENOX

Dear Healthcare Professional,

Teva Pharmaceuticals Ireland in agreement with the European Medicines Agency and the Health Products Regulatory Authority (HPRA) would like to inform you of the following:

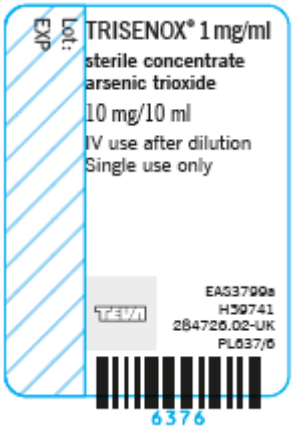
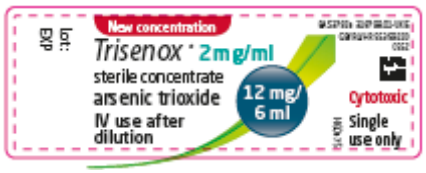
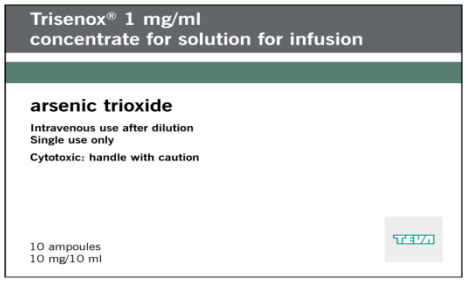
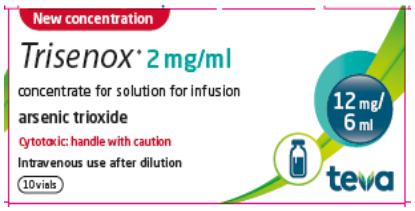
<u>Summary</u>

- **Risk for medication errors exists since TRISENOX (arsenic trioxide) will be replaced by a new presentation containing double concentration.**
    - **1 mg/ml single-use 10 ml ampoule (containing 10 mg of arsenic trioxide),**

      will be replaced by

    - **2 mg/ml single-use 6 ml vial (containing 12 mg of arsenic trioxide).**
- **The two different concentrations will temporarily coexist on the market and this may lead to mix-ups between the two products and to medication errors with either "overdosing" with potential fatal outcome or "underdosing" with potential lack of efficacy** *(see background section below).*
- **Always check carefully when calculating the dilution and infusion volume of TRISENOX to ensure that the patient receives the correct dose of arsenic trioxide.**
- **In order to help differentiate between the two presentations, the packages have distinctive features shown in the table below.**

Teva Pharmaceuticals Ireland
Digital Office Centre Swords, Suite 101 – 103, Balheary Demense, Balheary Road, Swords, Co. Dublin, K67E5AO | 1800 201 700

	Current presentation TRISENOX, 1 mg/ml, concentrate for solution for infusion	**New presentation** **TRISENOX, 2 mg/ml, concentrate for solution for infusion**
Concentration	1 mg/ml	**2 mg/ml**
Packaging unit	Ampoule of 10 ml	**Vial of 6 ml**
Arsenic Trioxide per container	10 mg	**12 mg**
Label of the immediate container		
Front side of the carton box		
Reconstitution	Both must be diluted with 100 to 250 ml of glucose 50 mg/ml (5%) solution for injection **or** sodium chloride 9 mg/ml (0.9%) solution for injection	

Teva Pharmaceuticals Ireland
Digital Office Centre Swords, Suite 101 – 103, Balheary Demense, Balheary Road, Swords, Co. Dublin, K67E5AO | 1800 201 700

Further information on the safety concern

TRISENOX (arsenic trioxide) is indicated for induction of remission, and consolidation in adult patients with:

- Newly diagnosed low-to-intermediate risk acute promyelocytic leukaemia (APL) (white blood cell count, ≤ 10 x 10^3/µl) in combination with all-*trans*-retinoic acid (ATRA).

- Relapsed/refractory acute promyelocytic leukaemia (APL) (previous treatment should have included a retinoid and chemotherapy) characterised by the presence of the t(15;17) translocation and/or the presence of the promyelocytic leukaemia/retinoic-acid-receptor-alpha (PML/RAR-alpha) gene.

The consequences of the medication errors due to a change in concentration of the available product on the market and mix-ups between the two presentations are:

- **Overdosing risk**: enhancement of one or all the known risks associated with the use of TRISENOX, which may result in **a potentially fatal outcome** from the following events:
  - Massive bleeding resulting from thrombocytopenia;
  - Severe infections, sepsis, and septic shock from severe leukopenia;
  - Cardiac arrest from QTc prolongation;
  - Acute promyelocytic leukemia (APL) differentiation syndrome;
  - Intracerebral bleeding or ischemic myocardial infarction from hyperleukocytosis;
  - Potential acute kidney injury or renal failure from enhanced nephrotoxicity;
  - Potential hepatic failure from enhanced elevations in liver transaminases, bilirubin, and gamma-glutamyl transferase.

Please refer to section 4.9 "overdosing" of the Summary of Product Characteristics (SmPC) describing how to manage overdosing.

- **Underdosing risk:** Suboptimal response to therapy resulting **in the possibility of cancer chemotherapy resistance with a reduced clinical response.**

If you have any additional questions about TRISENOX concentrate for solution for infusion, please contact Teva Medical Information on +44 20 540 7117 or via email to medinfo@tevauk.com.

Call for reporting:

Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance, website: www.hpra.ie. When reporting please provide as much information as possible, including information about medical history, any concomitant medication, onset, treatment dates, and product brand name. Adverse events should also be reported to Teva Pharmaceuticals Ireland by telephone to +44 207 540 7117 or via email to safety.ireland@teva.ie.

Yours Sincerely,

Tahir Saleem
Senior Medical Director Cluster Lead UK & IE

Teva Pharmaceuticals Ireland
Digital Office Centre Swords, Suite 101 – 103, Balheary Demense, Balheary Road, Swords, Co. Dublin, K67E5AO | 1800 201 700