# הודעה על החמרה ( מידע בטיחות)

**תאריך: 13.12.12**

**שם תכשיר באנגלית: TRISENOX 1 mg/ml**

**מספר רישום: 140-10-31787-00**

**שם בעל הרישום: מדיסון פארמה בע"מ**

השינויים בעלון מסומנים על רקע צהוב

בעלון לרופא

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| **פרטים על השינוי/ים המבוקש/ים** | | |
| **פרק בעלון** | **טקסט נוכחי** | **טקסט חדש** |
| **4.**2 **Posology and method of administration** | The same dose is recommended for children, adults, and elderly.  Consolidation schedule:  Consolidation treatment must begin 3 to 4 weeks after completion of induction therapy. TRISENOX is to be administered intravenously at a dose of 0.15 mg/kg/day for 25 doses given 5 days per week, followed by 2 days interruption, repeated for 5 weeks.  Paediatric use: The experience in children is limited. Of 7 patients under 18 years of age (range 5 to 16 years) treated with TRISENOX at the recommended dose of 0.15 mg/kg/day, 5 patients achieved a complete response. Safety and effectiveness in paediatric patients under 5 years of age have not been studied.  לא קיים.  לא קיים במיקום זה.  לא קיים במיקום זה.  **Method of administration**  TRISENOX must be administered intravenously over 1-2 hours. The infusion duration may be extended up to 4 hours if vasomotor reactions are observed. A central venous catheter is not required. Patients must be hospitalised at the beginning of treatment due to symptoms of disease and to ensure adequate monitoring. | The same dose is recommended for ~~children~~, adults, and elderly.  Consolidation schedule:  Consolidation treatment must begin 3 to 4 weeks after completion of induction therapy. TRISENOX is to be administered intravenously at a dose of 0.15 mg/kg/day for 25 doses given 5 days per week, followed by 2 days interruption, repeated for 5 weeks.  ~~Paediatric use: The experience in children is limited. Of 7 patients under 18 years of age (range 5 to 16 years) treated with TRISENOX at the recommended dose of 0.15 mg/kg/day, 5 patients achieved a complete response. Safety and effectiveness in paediatric patients under 5 years of age have not been studied.~~  Dose delay, modification and reinitiation  Treatment with TRISENOX must be interrupted, adjusted, or discontinued before the scheduled end of therapy at any time that a toxicity grade 3 or greater on the National Cancer Institute Common Toxicity Criteria is observed and judged to be possibly related to TRISENOX treatment. Patients who experience such reactions that are considered TRISENOX related must resume treatment only after resolution of the toxic event or after recovery to baseline status of the abnormality that prompted the interruption. In such cases, treatment must resume at 50% of the preceding daily dose. If the toxic event does not recur within 3 days of restarting treatment at the reduced dose, the daily dose can be escalated back to 100% of the original dose. Patients who experience a recurrence of toxicity must be removed from treatment.  For ECG and electrolytes abnormalities, see section 4.4.  Patients with hepatic and/or renal impairment  Since limited data are available across all hepatic impairment groups and across all renal impairment groups, caution is advised in the use of TRISENOX in patients with hepatic and/or renal impairment.  Paediatricpopulation  The safety and efficacy of TRISENOX in children aged up to 17 years has not been established. Currently available data for children aged 5 to 16 years are described in section 5.1 but no recommendation on a posology can be made. No data are available for children under 5 years.  **Method of administration**  TRISENOX must be administered intravenously over 1-2 hours. The infusion duration may be extended up to 4 hours if vasomotor reactions are observed. A central venous catheter is not required. Patients must be hospitalised at the beginning of treatment due to symptoms of disease and to ensure adequate monitoring.  For instructions on preparation of the medicinal product before administration, see section 6.6. |
| **4.3 Contraindications** | Hypersensitivity to arsenic or any of the excipients. | Hypersensitivity to the active substance or to any of the excipients listed in section 6.1. |
| **4.4 Special warnings and precautions for use** | Leukocyte Activation Syndrome (APL Differentiation Syndrome):twenty five percent of patients with APL treated with TRISENOX have experienced symptoms similar to a syndrome called the retinoic-acid-acute promyelocytic leukaemia (RA-APL) or APL differentiation syndrome, characterised by fever, dyspnoea, weight gain, pulmonary infiltrates and pleural or pericardial effusions, with or without leukocytosis.  Dose Modification:  Treatment with TRISENOX must be interrupted, adjusted, or discontinued before the scheduled end of therapy at any time that a toxicity grade 3 or greater on the National Cancer Institute Common Toxicity Criteria, Version 2 is observed and judged to be possibly related to TRISENOX treatment.  Patients who experience such reactions that are considered TRISENOX related must resume treatment only after resolution of the toxic event or after recovery to baseline status of the abnormality that prompted the interruption. In such cases, treatment must resume at 50% of the preceding daily dose. If the toxic event does not recur within 3 days of restarting treatment at the reduced dose, the daily dose can be escalated back to 100% of the original dose. Patients who experience a recurrence of toxicity must be removed from treatment.  Patients with renal impairment:  Caution is advised in the use of TRISENOX in patients with renal impairment.  In patients with severe renal impairment (creatinine clearance less than 30 mL/min), a dose reduction should be considered. The use of arsenic trioxide in patients on dialysis has not been studied.  Patients with hepatic impairment:  Since limited data are available across all hepatic impairment groups, caution is advised in the use of TRISENOX in patients with hepatic impairment. The experience in patients with severe hepatic impairment is insufficient to determine if dose adjustment is required. In patients with mild to moderate hepatic impairment, dose adjustment should not be necessary. | Leukocyte Activation Syndrome (APL Differentiation Syndrome):~~twenty five percent~~ 27% of patients with APL treated with TRISENOX have experienced symptoms similar to a syndrome called the retinoic-acid-acute promyelocytic leukaemia (RA-APL) or APL differentiation syndrome, characterised by fever, dyspnoea, weight gain, pulmonary infiltrates and pleural or pericardial effusions, with or without leukocytosis.  Dose delay and modification:  Treatment with TRISENOX must be  interrupted, adjusted, or discontinued before  the scheduled end of therapy at any time that  a toxicity grade 3 or greater on the National  Cancer Institute Common Toxicity Criteria is  observed and judged to be possibly related to  TRISENOX treatment.  ~~Patients who experience such reactions that are considered TRISENOX related must resume treatment only after resolution of the toxic event or after recovery to baseline status of the abnormality that prompted the interruption. In such cases, treatment must resume at 50% of the preceding daily dose. If the toxic event does not recur within 3 days of restarting treatment at the reduced dose, the daily dose can be escalated back to 100% of the original dose. Patients who xperience a recurrence of toxicity must be removed from treatment.~~  (see section 4.2)  Patients with renal impairment:  Since limited data are available across all renal impairment groups, caution is advised in the use of TRISENOX in patients with renal impairment.  ~~In patients with severe renal impairment (creatinine clearance less than 30 mL/min), a dose reduction should be considered. The use of arsenic trioxide in patients on dialysis has not been studied.~~  The experience in patients with severerenal impairment is insufficient to determine if dose adjustment is required.  The use of TRISENOX in patients on dialysis has not been studied.  Patients with hepatic impairment:  Since limited data are available across all hepatic impairment groups, caution is advised in the use of TRISENOX in patients with hepatic impairment. The experience in patients with severe hepatic impairment is insufficient to determine if dose adjustment is required. ~~In patients with mild to moderate hepatic impairment, dose adjustment should not be necessary.~~ |
| **4.6 Fertility, Pregnancy and lactation** | **Pregnancy and lactation**  **שינוי מקום בסעיף**  Arsenic trioxide has been shown to be embryotoxic and teratogenic in animal studies (see 5.3). There are no studies in pregnant women using TRISENOX.  If this medicinal product is used during pregnancy or if the patient becomes pregnant while taking this product, the patient must be informed of the potential harm to the foetus.  Men and women of childbearing potential must use effective contraception during treatment with TRISENOX.  Arsenic is excreted in human milk. Because of the potential for serious adverse reactions in nursing infants from TRISENOX, breastfeeding must be discontinued prior to and throughout administration. | **Fertility, pregnancy and lactation**  Contraception in males and females  Men and women of childbearing potential must use effective contraception during treatment with TRISENOX.  Pregnancy  Arsenic trioxide has been shown to be embryotoxic and teratogenic in animal studies (see section 5.3). There are no studies in pregnant women using TRISENOX. If this medicinal product is used during pregnancy or if the patient becomes pregnant while taking this product, the patient must be informed of the potential harm to the foetus.  ~~Men and women of childbearing potential must use effective contraception during treatment with TRISENOX.~~  Breastfeeding  Arsenic is excreted in human milk. Because of the potential for serious adverse reactions in nursing infants from TRISENOX, breastfeeding must be discontinued prior to and throughout administration.  Fertility  No clinical or non-clinical fertility studies have been conducted with TRISENOX. |
| **4.8 Undesirable effects** | Related adverse reactions of CTC grade 3 and 4 occurred in 37% of patients in clinical trials. The most commonly reported reactions were hyperglycaemia, hypokalaemia, neutropenia, and increased alanine amino transferase (ALT). Leukocytosis occurred in 50% of patients with APL, as determined by haematology assessments, rather than adverse events reports.  The table below lists the related grade 3 and 4 adverse drug reactions for the 107 patients treated with TRISENOX in clinical trials. (Frequencies defined as: common ≥1/100 to <1/10, uncommon ≥ 1/1,000 to < 1/100).  **לא קיים** | Related adverse reactions of CTC grade 3 and 4 occurred in 37% of patients in clinical trials. The most commonly reported reactions were hyperglycaemia, hypokalaemia, neutropenia, and increased alanine amino transferase (ALT). Leukocytosis occurred in 50% of patients with APL, as determined by haematology assessments, ~~rather than adverse events reports.~~  ~~The table below lists the related grade 3 and 4 adverse drug reactions for the 107 patients treated with TRISENOX in clinical trials. (Frequencies defined as: common ≥1/100 to <1/10, uncommon ≥ 1/1,000 to < 1/100).~~  The following undesirable effects have been reported in clinical trials and/or post-marketing experience. Undesirable effects are listed below as MedDRA preferred term by system organ class and frequencies observed during TRISENOX clinical trials in 52 patients with refractory/relapsed APL. Frequencies are defined as: very common≥1/10, common≥1/100 to <1/10, uncommon≥1/1000 to <1/100, not known (cannot be estimated from available data).  Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness. |

**טקסט קיים ( סעיף 4.8) :**

|  |  |  |
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| System Organ Class | Common | Uncommon |
| Blood and lymphatic system disorders | Neutropenia  Thrombocytopenia | Febrile neutropenia  Leucocytosis  Leucopenia |
| Metabolism and nutrition  disorders | Hyperglycemia Hypokalemia | Hypermagnesaemia Hypermatraemia Ketoacidosis |
| Nervous system disorders | Paraesthesia |  |
| Cardiac disorders |  | Pericardial effusion  Tachycardia |
| Vascular disorders |  | Vasculitis |
| Respiratory, thoracic and mediastinal disorders | Dyspnoea Pleuritic pain | Hypoxia Pleural effusion  Pulmonary alveolar Haemorrhage |
| Gastrointestinal disorders |  | Diarrhoea |
| Skin & subcutaneous tissue  disorders |  | Erythema Pruritus |
| Musculoskeletal and connective tissue disorders | Arthralgia  Bone pain | Myalgia |
| General disorders and  administration site conditions | Fatigue Pyrexia Oedema | Chest pain Pain |
| Investigations | ALT increased  Aspartate amino transferase increased  ECG QT prolonged | Hyperbilirubinaemia  Hypomagnesaemia |

**טקסט חדש – הטבלה הנ"ל הוחלפה בטבלה הבאה:**

|  | **All grades** | **Grades≥3** |
| --- | --- | --- |
| **Infections and Infestations** | | |
| Herpes zoster | Common | Not known |
| Sepsis | Not known | Not known |
| Pneumonia | Not known | Not known |
| **Blood and Lymphatic System Disorders** | | |
| Febrile neutropenia | Common | Common |
| Leukocytosis | Common | Common |
| Neutropenia | Common | Common |
| Pancytopenia | Common | Common |
| Thrombocytopenia | Common | Common |
| Anaemia | Common | Not known |
| Leukopenia | Not known | Not known |
| Lymphopenia | Not known | Not known |
| **Metabolism and Nutrition Disorders** | | |
| Hyperglycaemia | Very Common | Very Common |
| Hypokalaemia | Very Common | Very Common |
| Hypomagnesaemia | Very Common | Common |
| Hypernatraemia | Common | Common |
| Ketoacidosis | Common | Common |
| Hypermagnesaemia | Common | Not known |
| Dehydration | Not known | Not known |
| Fluid retention | Not known | Not known |
| **Psychiatric disorders** | | |
| Confusional state | Not known | Not known |
| **Nervous System Disorders** | | |
| Paraesthesia | Very Common | Common |
| Dizziness | Very Common | Not known |
| Headache | Very Common | Not known |
| Convulsion | Common | Not known |
| **Eye Disorders** | | |
| Vision blurred | Common | Not known |
| **Cardiac Disorders** | | |
| Tachycardia | Very Common | Common |
| Pericardial effusion | Common | Common |
| Ventricular extrasystoles | Common | Not known |
| Cardiac failure | Not known | Not known |
| Ventricular tachycardia | Not known | Not known |
| **Vascular Disorders** | | |
| Vasculitis | Common | Common |
| Hypotension | Common | Not known |
| **Respiratory, Thoracic and Mediastinal Disorders** | | |
| Differentiation syndrome | Very Common | Very Common |
| Dyspnoea | Very Common | Common |
| Hypoxia | Common | Common |
| Pleural effusion | Common | Common |
| Pleuritic pain | Common | Common |
| Pulmonary alveolar haemorrhage | Common | Common |
| Pneumonitis | Not known | Not known |
| **Gastrointestinal Disorders** | | |
| Diarrhoea | Very Common | Common |
| Vomiting | Very Common | Not known |
| Nausea | Very Common | Not known |
| Abdominal pain | Common | Common |
| **Skin and Subcutaneous Tissue Disorders** | | |
| Pruritus | Very Common | Not known |
| Rash | Very Common | Not known |
| Erythema | Common | Common |
| Face oedema | Common | Not known |
| **Musculoskeletal, Connective Tissue and Bone Disorders** | | |
| Myalgia | Very Common | Common |
| Arthralgia | Common | Common |
| Bone pain | Common | Common |
| **Renal and Urinary Disorders** | | |
| Renal failure | Common | Not known |
| **General Disorders and Administration Site Conditions** | | |
| Pyrexia | Very Common | Common |
| Pain | Very Common | Common |
| Fatigue | Very Common | Not known |
| Oedema | Very Common | Not known |
| Chest pain | Common | Common |
| Chills | Common | Not known |
| **Investigations** | | |
| Alanine amino transferase increased | Very Common | Common |
| Aspartate amino transferase increased | Very Common | Common |
| Electrocardiogram QT prolonged | Very Common | Common |
| Hyperbilirubinaemia | Common | Common |
| Blood creatinine increased | Common | Not known |
| Weight increased | Common | Not known |
| Gamma-glutamyltransferase increased\* | Not known\* | Not known\* |

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| **פרטים על השינוי/ים המבוקש/ים - המשך** | | |
| **פרק בעלון** | **טקסט נוכחי** | **טקסט חדש** |
| **4.**8 **Undesirable effects** | **לא קיים.**  During TRISENOX treatment, 13 of the 52 patients in the APL studies had one or more symptoms of APL differentiation syndrome, characterised by fever, dyspnoea, weight gain, pulmonary infiltrates and pleural or pericardial effusions, with or without leukocytosis (see section 4.4).  The following adverse events have been identified during the post-approval use of TRISENOX and have been included following consideration of the observed frequency, seriousness and possible causal relationship to TRISENOX. All occurred with a frequency of uncommon (≥1/1,000 to <1/100). | \**In the CALGB study C9710, 2 cases of grade ≥3 increased GGT were reported out of the 200 patients who received TRISENOX consolidation cycles (cycle 1 and cycle 2) versus none in the control arm.*  During TRISENOX treatment, 14 of the 52 patients in the APL studies had one or more symptoms of APL differentiation syndrome, characterised by fever, dyspnoea, weight gain, pulmonary infiltrates and pleural or pericardial effusions, with or without leukocytosis (see section 4.4).  ~~The following adverse events have been identified during the post-approval use of TRISENOX and have been included following consideration of the observed frequency, seriousness and possible causal relationship to TRISENOX. All occurred with a frequency of uncommon (≥1/1,000 to <1/100).~~ |

**הטבלה מטה הוסרה:**

|  |  |
| --- | --- |
| System Organ Class | Uncommon |
|
| Infection and Infestations | Sepsis  Pneumonia  Herpes zoster |
| Blood and Lymphatics System Disorders | Anaemia |
| Metabolism and Nutrition Disorders | Dehydration  Fluid retention |
| Psychiatric Disorders | Confusional state |
| Nervous System Disorders | Convulsions  Dizziness |
| Eye Disorders | Vision blurred |
|
| Cardiac Disorders | Cardiac failure  Ventricular tachycardia  Ventricular extrasystoles |
| Vascular Disorders | Hypotension |
| Respiratory, Thoracic and Mediastinal Disorders | Pneumonitis |
| Gastrointestinal Disorders | Vomiting  Abdominal pain |
| Skin and Subcutaneous Disorders | Face oedema  Rash |
| Renal and Urinary Disorders | Renal failure |
| General Disorders and Administration Site  Conditions | Oedema  Chills |
| Investigations | Blood creatinine increased  Weight increased |

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| **פרטים על השינוי/ים המבוקש/ים - המשך** | | |
| **4.8 Undesirable effects** | In post marketing experience, pancytopenia has been reported; a differentiation syndrome, like retinoic acid syndrome, has also been reported with the use of TRISENOX for the treatment of malignancies other than APL. | In post marketing experience, ~~pancytopenia has been reported;~~ a differentiation syndrome, like retinoic acid syndrome, has also been reported ~~with the use of TRISENOX~~ for the treatment of malignancies other than APL with TRISENOX. |
| **4.9 Overdose** | Thereafter, penicillamine at a daily dose ≤ 1 gm per day may be given. In the presence of coagulopathy, the oral administration of the chelating agent Dimercaptosuccinic Acid Succimer (DCI) 10 mg/kg or 350 mg/m2 every 8 hours during 5 days and then every 12 hours during 2 weeks is recommended. | Thereafter, penicillamine at a daily dose ≤ 1 gm per day may be given. In the presence of coagulopathy, the oral administration of the chelating agent Dimercaptosuccinic Acid Succimer (DCI) 10 mg/kg or 350 mg/m2 every 8 hours during 5 days and then every 12 hours during 2 weeks is recommended. For patients with severe, acute arsenic overdose, dialysis should be considered. |
| **5.1 Pharmacodynamic properties** | TRISENOX has been authorised under “Exceptional Circumstances”. This means that due to the  rarity of the disease, it has not been possible to obtain complete information on this medicinal product.  The European Medicines Agency (EMEA) will review any new information which may become available every year and this SPC will be updated as necessary. | ~~TRISENOX has been authorised under “Exceptional Circumstances”. This means that due to the~~  ~~rarity of the disease, it has not been possible to obtain complete information on this medicinal product.~~  ~~The European Medicines Agency (EMEA) will review any new information which may become available every year and this SPC will be updated as necessary.~~ |

**גרף קיים ( סעיף 5.1) :**



**הגרף הנ"ל הוסר ובמקומו הוכנס הגרף הבא:**

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| **פרטים על השינוי/ים המבוקש/ים - המשך** | | |
| **5.1 Pharmacodynamic properties** | **שינה מקום, הועבר מסעיף 4.2** | Paediatric population  The experience in children is limited. Of 7 patients under 18 years of age (range 5 to 16 years) treated with TRISENOX at the recommended dose of 0.15 mg/kg/day, 5 patients achieved a complete response (see section 4.2). |
| **5.2 Pharmacokinetic properties** | In vitro enzymatic studies with human liver microsomes revealed that arsenic trioxide has no inhibitory activity on substrates of the major cytochrome P450 enzymes such as 1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, 3A4/5, 4A9/11. Drugs that are substrates for these P450 enzymes are not expected to interact with TRISENOX.  **Linearity/non-linearity:**  In the total single dose range of 7 to 32 mg (administered as 0.15 mg/kg), systemic exposure (AUC) appears to be linear. The decline from peak plasma concentration of AsIII occurs in a biphasic manner and is characterized by an initial rapid distribution phase followed by a slower terminal elimination phase. After administration at 0.15 mg/kg on a daily (n=6) or twice-weekly (n=3) regimen, an approximate 2-fold accumulation of AsIII was observed as compared to a single infusion. This accumulation was slightly more than expected based on single-dose results. | **שינוי מקום בתוך הסעיף**  **שינוי מקום בתוך הסעיף** |
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