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PRESCRIBING ALERT®

Dear Healthcare Professional,

At *MPR* we strive to bring you important drug information in a concise and timely fashion. In keeping with this goal, we are pleased to bring you this PRESCRIBING ALERT for VALSTAR® (valrubicin) 200 mg/5 mL Sterile Solution for Intravesical Instillation, from Endo Pharmaceuticals.

VALSTAR, a chemotherapeutic anthracycline, is the only FDA-approved intravesical therapy for bacillus Calmette-Guérin (BCG)-refractory carcinoma *in situ* (CIS) of the urinary bladder when immediate cystectomy would be associated with unacceptable morbidity or mortality.[1] Patients with an unacceptable risk of morbidity or mortality may include the elderly and those with cardiovascular or cerebrovascular disease, clotting disorders, arrhythmias, impaired pulmonary function, and concurrent malignancy.[2,3]

VALSTAR is recommended at a dose of 800 mg administered intravesically once a week for 6 weeks.[1] Administration should be delayed at least 2 weeks after transurethral resection and/or fulguration. Patients should retain the drug for 2 hours before voiding.[1]

Important Safety Information
VALSTAR® is contraindicated in patients with known hypersensitivity to anthracyclines or polyoxyl castor oil. VALSTAR should not be administered to patients with a perforated bladder, compromised bladder mucosa integrity, concurrent urinary tract infections, or small bladder capacity (unable to tolerate a 75 mL instillation). The integrity of the bladder should be confirmed prior to instillation of VALSTAR in those patients who have had procedures with the potential to compromise the bladder wall.

Patients should be informed that VALSTAR has been shown to induce complete response in about 1 in 5 patients with BCG-refractory CIS. Delaying cystectomy could lead to development of metastatic bladder cancer. **If there is not a complete response of CIS to treatment after 3 months or if CIS recurs, cystectomy must be reconsidered.**

VALSTAR should be administered using aseptic technique under the supervision of a practitioner experienced in the use of intravesical cancer chemotherapeutic agents. VALSTAR should be used with caution in patients with severe irritable bladder symptoms. Patients of reproductive age should be advised to use an effective contraception method.

(Important Safety Information continued on next page)

Important Safety Information (continued)
In clinical trials, the most common local adverse events include urinary frequency, urinary urgency, and dysuria. The most common systemic adverse events include urinary tract infection, abdominal pain, nausea, asthenia, headache, malaise, and urinary retention.

Patients receiving VALSTAR® must be closely monitored for disease recurrence or progression. The recommended evaluation should include cystoscopy, biopsy, and/or urine cytology every 3 months.

More information about the use of VALSTAR is available at www.valstarsolution.com.

For your reference, please see the full Prescribing Information for VALSTAR.

Sincerely,

Grace L. McBride
Editorial Director
MPR Custom Programs

REFERENCES

1. VALSTAR [package insert]. Chadds Ford, PA: Endo Pharmaceuticals, Inc.; April 2009.

2. Marchetti A, Wang L, Magar R, et al. Management of patients with Bacilli Calmette-Guérin-refractory carcinoma in situ of the urinary bladder: cost implications of a clinical trial for valrubicin. *Clin Ther.* 2000;22(4):422-438.

3. Steinberg G, Bahnson R, Brosman S, et al; and Valrubicin Study Group. Efficacy and safety of valrubicin for the treatment of Bacillus Calmette-Guerin refractory carcinoma in situ of the bladder. *J Urol.* 2000;163(3):761-767.

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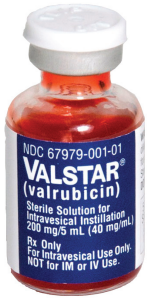
PRESCRIBING ALERT

VALSTAR® (valrubicin)

200 mg/5 mL Sterile Solution for Intravesical Instillation

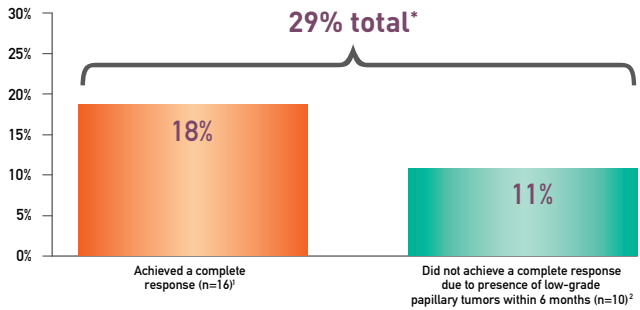
Company: Endo Pharmaceuticals ℞
Pharmacologic Class: Anthracycline
Active Ingredient: Valrubicin 40 mg/mL in 50% polyoxyl castor oil/50% dehydrated alcohol, USP.
Indication: Intravesical therapy of BCG-refractory carcinoma *in situ* (CIS) of the urinary bladder in patients for whom immediate cystectomy would be associated with unacceptable morbidity or mortality.
Dosage and Administration: 800 mg intravesically once weekly for 6 weeks. Retain in bladder for 2 hours before voiding. Maintain adequate hydration.
Adverse Reactions: Local: urinary frequency, urinary urgency, dysuria; Systemic: UTI, abdominal pain, nausea, asthenia, headache, malaise, urinary retention.



VALSTAR Intravesical Therapy

Only FDA-approved intravesical therapy indicated for BCG-refractory CIS of the urinary bladder in patients for whom immediate cystectomy would be associated with unacceptable morbidity or mortality[1]

PATIENTS WERE JUDGED TO HAVE DERIVED A CLINICAL BENEFIT FROM VALSTAR®



Study design: Three-year, open-label, noncomparative study. Forty-four investigators at 41 sites enrolled 90 patients with pathologically proven CIS. Patients were to have received at least 2 prior courses of intravesical therapy for CIS, including at least 1 course of BCG. Each patient was scheduled to receive 800 mg of VALSTAR once a week for 6 weeks. Primary disease evaluation took place 6 weeks after the last instillation of VALSTAR. Subsequent evaluations for disease response occurred at 3-month intervals.[2]

*18% of patients (16) achieved the primary end point of complete response (ie, were disease-free at both 3 and 6 months after treatment initiation). An additional 11% of patients (10), who did not achieve a complete response at 6 months, were determined to have benefited from treatment because they had low-grade papillary tumors (Ta). Together, these account for 29% of patients deriving a clinical benefit from VALSTAR treatment.[1,2]

Important Safety Information

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PRESCRIBING ALERT

- **18% of patients (n=16) were disease-free at both 3 and 6 months[1,2,†]**
- **29% of patients were judged to have derived a clinical benefit from VALSTAR® treatment[1,2]**
  - 11% of patients (n=10) did not achieve a complete response due to the presence of low-grade papillary tumors within 6 months[2]
- **Durable efficacy among complete responders[1,†]**
  - Median of 13.5 months from start to treatment to last negative biopsy[1]
  - Median of 21 months from start of treatment until first documented recurrence[1]
- **Demonstrated safety profile in clinical trials**
  - 2% of patients discontinued therapy due to local bladder symptoms[3,‡]
  - Most local bladder adverse reactions were mild to moderate and resolved within 1 to 7 days[1,2]

†Complete response defined as disease free at both 3 and 6 months after treatment initiation.
‡Based on the pivotal clinical study.

Important Safety Information (continued)

- Patients should be informed that VALSTAR has been shown to induce complete response in about 1 in 5 patients with BCG-refractory CIS. Delaying cystectomy could lead to development of metastatic bladder cancer. **If there is not a complete response of CIS to treatment after 3 months or if CIS recurs, cystectomy must be reconsidered**.
- VALSTAR should be administered using aseptic technique under the supervision of a practitioner experienced in the use of intravesical cancer chemotherapeutic agents. VALSTAR should be used with caution in patients with severe irritable bladder symptoms. Patients of reproductive age should be advised to use an effective contraception method.
- In clinical trials, the most common local adverse events include urinary frequency, urinary urgency, and dysuria. The most common systemic adverse events include urinary tract infection, abdominal pain, nausea, asthenia, headache, malaise, and urinary retention.
- Patients receiving VALSTAR must be closely monitored for disease recurrence or progression. The recommended evaluation should include cystoscopy, biopsy, and/or urine cytology every 3 months.

Please see full Prescribing Information.

REFERENCES

1. VALSTAR [package insert]. Chadds Ford, PA: Endo Pharmaceuticals, Inc.; October 2009.
2. Steinberg G, Bahnson R, Brosman S, et al; and the Valrubicin Study Group. Efficacy and safety of valrubicin for the treatment of Bacillus Calmette-Guerin refractory carcinoma in situ of the bladder. *J Urol.* 2000;163(3): 761-767.
3. Data on file, DOF-VL-06. Endo Pharmaceuticals; 2009.

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