# Clinical Pharmacy News Letter

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## BYVALSON (NEBIVOLOL AND VALSARTAN)

Company : Allergan

Approval Status : Approved June 06 2016

Specific Treatments : Hypertension

Therapeutic Areas : Cardiology/vascular diseases

Byvalson (nebivolol and valsartan 5 mg/ 80 mg tablet) is a fixed-dose combination of nebivolol - a beta-adrenergic receptor blocking agent that is preferentially beta-1 selective, and valsartan - an angiotensin II receptor blocker. It is specifically indicated for the treatment of hypertension, to lower blood pressure. This drug is supplied as a tablet for oral administration. The recommended dose is as follows: as initial therapy and in patients not adequately controlled on valsartan 80 mg or nebivolol up to and including 10 mg, the recommended dose is 5 mg/ 80 mg taken orally once daily. Maximum antihypertensive effects are attained within 2 to 4 weeks. Byvalson may be substituted for its components in patients already receiving 5 mg nebivolol and 80 mg valsartan.

**FDA Approval:** The FDA approval of Byvalson was based on a Phase III, double-blind, placebo-controlled, dose-escalating, 8-week efficacy and safety study, which randomized approximately 4,100 patients with Stage 1 or 2 hypertension. Treatment with Byvalson 5 mg/ 80 mg for 4 weeks resulted in placebo-adjusted reductions from baseline in systolic (SBP) and diastolic (DBP) blood pressure of -8.3 and -7.2 mmHg, respectively. Treatment with Byvalson 5 mg/ 80 mg resulted in greater reductions in SBP and DBP than did treatment with nebivolol 5 mg alone ($p<0.0001$ for both SBP and DBP) or valsartan 80 mg, alone ($p=0.0007$ for SBP and $p<0.0001$ for DBP). The overall rate of adverse events was similar across treatment groups and placebo during this 4

week period. **Side effects:** Adverse effects associated with the use of Byvalson may include, but are not limited to, the following: Skull hypoplasia, Anuria, Hypotension, Renal failure,Death Byvalson comes with a Black Box warning of fetal toxicity. When pregnancy is detected, discontinue Byvalson as soon as possible. Drugs, including Byvalson, that act directly on the rennin angiotensin system can cause injury and death to the developing fetus. **Mechanism of action:** Byvalson (nebivolol and valsartan 5 mg/ 80 mg tablet) is a fixed-dose combination that combines two FDA approved, once daily, blood pressure lowering agents with different mechanisms of action. Nebivolol is a beta-adrenergic receptor blocking agent that is preferentially beta-1 selective. Valsartan is an angiotensin II receptor blocker (ARB) that blocks the binding of angiotensin II to the AT1 receptor in many tissues, such as vascular smooth muscle and the adrenal gland, thereby blocking its vasoconstrictor and aldosterone-secreting effects.

**Carbamazepine**

**Risk of Stevens Johnson's Syndrome.**

The Central Drugs Standard Control Organisation (CDSCO) and the Signal Review Panel of the Pharmacovigilance Programme of India-Indian Pharmacopoeia (SRP-PvPI-IPC) have requested that all manufacturers of carbamazepine should include Stevens Johnson's Syndrome as an adverse reaction in the package inserts and on the official websites.

Carbamazepine is used as an anticonvulsant used in patients with epilepsy and in patients with trigeminal neuralgia. In India, there are 122 reports of life threatening or fatal skin reactions (Stevens Johnson's Syndrome, Toxic Epidermal Necrolysis) that may have been caused by the use of carbamazepine formulations. Although Stevens Johnson's Syndrome is a known adverse effect of carbamazepine and is already included in some package inserts, the Subject Expert Committee (SEC) have recommended that all manufacturers should include the same information on this adverse effect. The CDSCO/PvPI have decided that it was necessary to revise the package insert to include screening of HLA-B* 1502 prior to initiating the carbamazepine treatment, as HLA-B* 1502 is a known factor for carbamazepine-induced Stevens Johnson's Syndrome.

***Reference:*** Central Drugs Standard Control Organisation, February 2016 (www.cdsco.nic.in)

**Piperacillin and tazobactam combination: Risk of Bronchospasm and Hsypokalaemia**

The CDSCO has requested that bronchospasm and hypokalaemia are included as adverse reactions in the package insert for combination products of piperacillin and tazobactam. The request follows the recommendation received from the Pharmacovigilance Programme of India - Indian Pharmacopoeia Commission (PvPI-IPC). Piperacillin and tazobactam are used as antibiotics in combination. Based on available evidence and advice of the subject expert committee, CDSCO/PvPI have decided that it was necessary to revise the package insert to add hypokalaemia and bronchospasm as clinically significant adverse reactions.

***Reference:*** Central Drugs Standard Control Organisation, February 2016 (www.cdsco.nic.in)

**Possible causal relationship between levetiracetam and impaired renal function**

Based on information derived from Individual Case Safety Reports (ICSRs) available in the WHO Global database of ICSRs, VigiBase® WHO has published causal relationship between levetiracetam and interstitial nephritis in the current news letter. Nine cases supported the hypothesis of a possible causal relationship between levetiracetam and impaired renal function. The pharmacological mechanism behind this signal needs to be further elucidated.

**Reference:** WHO Pharmaceuticals Newsletter No. 2, 2016 18-23

Renal failure and interstitial nephritis reported with single suspect levetiracetam: nine cases with a positive dechallenge

| Case | Age/ Sex | Suspected (S) or concomitant (C) drugs | Indication | Daily dose | Reactions (WHO-ART preferred terms) | Time to onset | Dechallenge outcome/ Comments |
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| 14 | 17/F | Levetiracetam (S) | Convulsion | 500 mg | Renal failure acute, abdominal pain, diarrhoea, fatigue, nephritis interstitial, pallor, renal function abnormal, vomiting | 10 days | Reaction abated after drug withdrawal and corticosteroid treatment. No history of renal problems and no other medications. Changed antiepileptic treatment to |

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| | | | | | Back pain, urinary tract stenosis and hydronephrosis were diagnosed after withdrawal of drug. | | oxcarbamazepine. |
| 28 | 12/F | Levetiracetam (S) | Epilepsy | - | Renal failure acute, acidosis, confusion, drug level increased, dyspnoea, EEG abnormal, encephalopathy, medicine ineffective, muscle contractions involuntary, somnolence, tremor | - | Patient returned to baseline after drug withdrawal. Unclear why she was admitted for acute renal failure. Had a history of Chiari II, myelomeningocele, shunted hydrocephalus, renal tubular acidosis and well-controlled epilepsy on levetiracetam. |
| 3 | 6 weeks/F | Levetiracetam (S) | Seizure | 54 mg | Renal failure acute | 16 days | Reaction abated after drug withdrawal. Prematurity could contribute to susceptibility. Renal failure reported as transient. |
| 4 | 73/M | Levetiracetam (S) Gliclazide, losartan, aspirin (all C) | Epilepsy | - | Renal failure acute, nephritis | 1 day | Reaction abated after drug withdrawal. The patient had a history of arterial hypertension and Type 2 diabetes mellitus, and a long-time |

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| | | | | | | | treatment with glicazide, losartan and aspirin. Losartan is known to cause renal failure. |
| 5 | 21/M | Levetiracetam (S) | Epilepsy | 250 mg for some weeks, increased to 500 mg | Renal failure acute | ~20 days | Reaction abated after drug withdrawal. |
| 6 | 60/F | Levetiracetam (S) | Petit mal epilepsy | 500 mg | Renal failure acute | 4 days | Reaction abated after drug withdrawal. |
| 7 | 20/M | Levetiracetam (S) | - | 750 mg and 1000 mg | Nephritis interstitial | - | Reaction abated after drug withdrawal. Dates were not given for the different dosages. |
| 8 | 45/F | Levetiracetam (S) | Epilepsy | 1000 mg | Nephritis interstitial, renal acidosis tubular | - | Reaction abated after drug withdrawal. |
| 99 | 45/M | Levetiracetam (S) Dexamethasone, temozolomide (both C) | Seizure prophylaxis | 1000 mg start dose increased over a 2-month period to 3000 mg | Nephritis interstitial, renal failure acute | 2 months | Reaction abated after drug withdrawal. Levetiracetam was changed to lacosamide and patient improved clinically and the creatinine normalized over 1 month. |

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