

## ADVICE TO GPs FOR PATIENTS DISCHARGED ON A COMBINATION OF VENLAFAXINE AND MIRTAZAPINE

### Theory for combination:

- Venlafaxine and its active metabolite inhibit synaptosomal reuptake of serotonin, noradrenaline and to a lesser extent dopamine to produce their antidepressant effect.
- Mirtazapine is a centrally active pre-synaptic alpha-<sub>2</sub>-antagonist, which increases central noradrenergic and serotonergic neurotransmission.

Noradrenaline neurotransmission is partly under the control of presynaptic alpha-<sub>2</sub>-adrenergic autoreceptors which when stimulated by noradrenaline inhibit the release of noradrenaline into the synapse. There are other alpha-<sub>2</sub>-receptors (heteroreceptors) located on the presynaptic terminal end of serotonergic neurons which when stimulated by noradrenaline inhibit the release of serotonin. Blockade of these receptors would prevent this inhibition.

Therefore it is thought that mirtazapine enhances noradrenaline and serotonin transmission by blockade of these receptors. And thus augmentation of venlafaxine with mirtazapine is due to a synergistic effect on serotonergic systems.

### Interactions:

Using combinations of serotonergic antidepressants increases the risk of developing serotonin syndrome. Where the patient is routinely prescribed any physical medicines that act on the serotonin system e.g. triptans, tramadol, St John's Wort, a discussion should occur between the prescriber and the GP to ensure that these medicines are reviewed.

Serotonin syndrome is a potentially dangerous adverse reaction that is attributed to a toxic hyper-serotonergic state from hyper-stimulation of the brain stem and 5HT<sub>1A</sub> and 5HT<sub>2</sub> receptors. Onset is usually within a few hours of drug or dose changes.

Symptoms of serotonin syndrome include and are usually a combination of at least three of the following:

- Mental state changes e.g. confusion, poor co-ordination, hypomania
- Agitation/Restlessness
- Tremor
- Sweating, fever, shivering
- Gastro intestinal side effects e.g. diarrhoea
- Hypertension
- Tachycardia
- Convulsions

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Ensure all other causes have been ruled out e.g. infection, metabolic disturbances, substance misuse or withdrawal.

**Monitoring:**

The Summary of Product Characteristics of Efexor (venlafaxine) states that all patients should be carefully screened for high blood pressure and pre-existing hypertension should be controlled before initiation of treatment. It also recommends that blood pressure should be reviewed periodically, after initiation of treatment and after each dose increase of venlafaxine. Therefore it would be prudent to do the same with the combination.

However there are no guidelines available as to specific frequency of blood pressure monitoring nor is there guidance on specific actions to be taken if blood pressure increases. Locally a decision has been made that if there is an increase of greater than 10mm of mercury or BP reading is above 140 / 90 on two consecutive readings, advice should be sought from the consultant psychiatrist on treatment options. In all cases a risk/benefit discussion needs to take place with the patient, GP and Specialist to decide the safest option with regards to both mental and physical health.

Patient specific monitoring will be detailed in the accompanying clinic letter.

This leaflet has been produced using information from a number of sources. It is intended to be a summary of available information. For more detailed prescribing information please refer to the summary of product characteristics ([www.medicines.org.uk](http://www.medicines.org.uk)).

Prepared by NHFT Medicines Management Committee September 2011.

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