VENLAFAXINE (EFEXOR)
SUMMARY OF BASIS FOR REGULATORY POSITION

1. Introduction

Data from the Office of National Statistics from 1993-2002 have demonstrated a significantly higher rate of fatal overdose (fatal toxicity index) with the antidepressant venlafaxine, when compared with selective serotonin reuptake inhibitor class (SSRIs). The fatal toxicity index data, together with concerns that venlafaxine may produce life-threatening cardiotoxicity resulted in regulatory action in December 2004 to restrict usage. The Marketing Authorisation (MA) holder has disputed the scientific basis for this action and has engaged in an appeal process. This report summarises the Medicines and Healthcare products Regulatory Agency (MHRA) current regulatory position on venlafaxine and the scientific basis for that position.

2. Dose-related toxicity of venlafaxine

Venlafaxine is a selective serotonin and noradrenaline reuptake inhibitor (SNRI) antidepressant, and is associated with a number of dose-related toxicities, which are described in the SPC. Many of these (such as nausea, sweating, tremor, agitation, anorexia, dizziness etc) are issues of tolerability rather than safety. Similarly, most rare and very rare side effects (such as thrombocytopaenia, and blood dyscrasias) are idiosyncratic reactions and are not dose-related. Whilst venlafaxine has many side effects in common with SSRI antidepressants, its tolerability profile is not identical, and (compared to some SSRIs) it may be associated with a higher rate of some side effects, such as nausea, dizziness, headache and withdrawal reactions. Venlafaxine may even differ somewhat from other members of the SNRI class (for example in relation to the frequency of hypertension-related reactions).

Venlafaxine has been shown to be toxic and potentially fatal in mixed and single overdoses. Overall, approximately 10% of venlafaxine overdoses reported to the company have proven fatal. The case fatality rate in the UK ADROIT database for single overdoses (which are more informative about toxicity) has been higher ~27%. The case fatality rate will depend to some extent on the pattern of reporting; if only large/serious overdoses are reported then the case fatality rate will be higher than if relatively modest overdoses are reported.

The majority of reported non-fatal overdoses have involved quantities < 2.5 grams, but some patients have survived in excess of 10 grams. Company data (2002) indicate that approximately 57% of overdoses have involved more than one drug, whereas in the UK (ONS data) the figure is 67%. Most fatal cases of single overdose have not stated the amount ingested, but doses as low as 2 grams have proven fatal.

Many factors might account for wide range of fatal and non-fatal doses, such as individual pharmacodynamic and pharmacokinetic susceptibility, time to presentation and access to medical care. Most of the cases of single overdose fatality have not provided a cause of death, or dose ingested, but for the few cases where a cause has been cited, this has generally been either CNS effects (such as seizure, or coma), or cardiac effects (arrhythmia, cardiac arrest).

2.1 Individual toxicities that might lead to overdose fatality

Evidence from pre-clinical/in vitro models, clinical trials and post-marketing ADR reports suggests that venlafaxine may, rarely, produce cardiotoxicity in overdose. Evidence relating to Na^+ channel and K^+ channel blockade is controversial, but such effects could be clinically relevant a very high doses in susceptible individuals. Reports of ventricular arrhythmia at therapeutic doses are very rare and many are 'confounded' by pharmacodynamic risk factors for cardiac events. This may suggest that venlafaxine is purely coincidental in these cases, but could indicate that the drug can trigger serious arrhythmia in those who are already predisposed.

Analyses of the company data, UK spontaneous adverse drug reaction (ADR) data, collected through the Yellow Card Scheme ('ADROIT' database), and scientific literature suggest that there are various other mechanisms by which venlafaxine could theoretically prove fatal in overdose; including seizure, serotonin syndrome (sometimes with severe muscle toxicity), and CNS depression. However it is not clear how often these may have contributed to or caused death.

Blood pressure (BP) increases are common in therapeutic doses, but severe increases in BP are usually accompanied by other risk factors, and do not appear to be a significant feature of overdose. Likewise, haemorrhagic stroke (which may be caused by a

combination of high BP and a bleeding diathesis, secondary to reduced platelet function) appears to occur only very rarely, although the rate in elderly patients may be greater.

The issue of possible drug-induced suicidality with the SSRI and related antidepressants has been the subject of a thorough investigation by an Expert Working Group of the former Committee on Safety of Medicines. Trial data show increased risks associated with the use of venlafaxine and most SSRIs antidepressants in children. Clinical trials in adults have not been powered to detect changes in suicidal behaviour, and it is not possible to rule-out an increased risk in some susceptible individuals. Given the identified risk in children/adolescents, it is probable that some increased risk remains present in young adults, and the venlafaxine clinical trial data are tentatively suggestive of a possible increased risk in the 18-29 year age-group. Although this issue relates to therapeutic treatment, rather than overdose toxicity, any differences between drugs may result in differences in observed fatality rates.

2.2 Interpatient variability in susceptibility to venlafaxine toxicity

There are no clear explanations for why some patients have survived massive overdoses of venlafaxine and others have died after taking lower doses. However, it is likely that patients with baseline pharmacodynamic risk factors (e.g. medical history or concomitant medication) relating to cardiac arrhythmia, seizure, serotonin syndrome, CNS depression or increased blood pressure may be more prone to venlafaxine's harmful effects.

Pharmacokinetic/genetic variability might also account for differences in responses to venlafaxine overdose. CYP2D6 poor metabolisers (PMs) have higher exposure to venlafaxine, and lower exposure to its principal metabolite (ODV). As CYP3A4 also plays a minor role in venlafaxine metabolism, it is not surprising that the combination of CYP2D6 PM status and potent CYP3A4 inhibition can result in yet higher exposure to venlafaxine (although the limited available evidence suggests that individual responses may be quite variable). There is no conclusive evidence that pharmacokinetic variability has led to meaningful increases in toxicity, however as the relative toxicity of venlafaxine and ODV are largely unknown, an increased risk associated with PM status and CYP3A4 inhibition cannot be ruled out.

The ratio between the lowest recorded fatal dose (~2g) and the highest therapeutic daily dose (375mg) is only 5.33, and it is therefore conceivable that PM status/CYP3A4 inhibition could (in rare individuals) be significant even at high therapeutic doses. However, it must be borne in mind that doses >10g have proven non-fatal, and that there is very little evidence to substantiate this potential risk.

As the majority of overdoses involve either alcohol or other drugs, possible interactions leading to increased toxicity may be of vital importance in relation to fatality rates. However, there are relatively few data on such interactions.

3. Toxicity of venlafaxine versus SSRIs and TCAs

Comparisons of recorded deaths attributed to drug overdose have been compared with prescribing data to calculate fatal toxicity indices (FTI), in the UK. In such analyses TCAs (in particular dothiepin) have been associated with a higher FTI than venlafaxine, which in turn has been associated with a higher FTI than SSRIs.

3.1 Toxicity of venlafaxine versus TCAs

The relatively high FTI for TCAs is not unexpected, as these drugs have long been understood to be potentially lethal in overdose. TCAs product information warns about possible tachyarrhythmia, hypotension, seizures, metabolic disturbances and other serious effects. The relative safety of TCAs, and the possible need for regulatory action (especially in relation to dothiepin) warrants further detailed examination, but this is not the focus of the current report. Although biases may have affected the FTI for TCAs in the published analyses to some extent, it would be reasonable to conclude that venlafaxine is generally less toxic than this class of antidepressant in overdose.

3.2 Toxicity of venlafaxine versus SSRIs

Published data show a higher FTI for venlafaxine versus SSRIs, both in relation to mixed and single overdoses (with or without alcohol). The difference in single overdose rates is more informative about possible toxicity, and in the ONS dataset this was 8.5 deaths per million prescriptions (venlafaxine) versus 1.0 death per million prescriptions (combined SSRIs). However, there was some heterogeneity in the SSRI data, and citalopram was noted to have a somewhat higher FTI than other members of the

class. The possible explanations for the different FTI data for venlafaxine versus SSRIs include differences in

- Prescription duration
- Efficacy
- Treatment discontinuations
- Drug-induced suicidality
- Selection biases (resulting in venlafaxine patients having a higher baseline suicidality risk)
- Drug induced toxicity
- A combination of factors

The available evidence does not suggest that differences in prescription duration, efficacy or treatment discontinuation rates are likely to contribute to the higher FTI for venlafaxine.

The data are inadequate to exclude the possibility that differences in drug-induced suicidality between venlafaxine and SSRIs may be a factor contributing towards the overall fatality rates; however any effect is likely to be small.

The pattern of prescribing (by indication) is broadly similar for venlafaxine and SSRIs, however data from DINlink and GPRD are supportive of significant differences in patient selection for the treatment of depression. Venlafaxine-treated patients are more likely to be receiving treatment as 2nd, 3rd, or 4th line treatment than SSRIs, and to have other baseline risk-factors for suicide. Data from GPRD suggest that such differences might account for (approximately) a 2-fold increase in suicidal behaviour (versus citalopram and fluoxetine), although the actual increased risk may be less, as the risk ratio was still elevated after adjustment for risk factors. The magnitude of the increased baseline risk of suicidality revealed in GPRD and ADROIT would not appear to account for the 8.5 fold increase in FTI for single overdoses.

In the absence of any other reasonable explanation, it would be appropriate to conclude that an increase in toxicity might account for the higher FTIs for venlafaxine. This is also supported by a higher case fatality rate for venlafaxine in single drug overdoses in ADROIT (with the exception of the rate for citalopram). The ADROIT single drug overdose case-fatality rates appear to be parallel to the published FTI data (TCAs higher than venlafaxine higher than SSRIs –although the rate for citalopram was similar to

venlafaxine). Further support for a higher risk of life-threatening toxicity comes from the US Drug Abuse Warning Network (DAWN) database, in which a higher proportion of suicide attempts resulted in admission to Intensive Care Units (ITUs) for venlafaxine than SSRIs. However it is important to note that admission to ITU in relation to specific drug overdoses may have been subject to biases, for example it is possible that greater concern over venlafaxine overdose might lead to a lower threshold for admission to such units.

Overall, the most plausible explanation for the differences in published FTIs, is a combination of increased toxicity and some baseline confounding by suicidal risk factors, however the evidence is not conclusive. There are insufficient data to rule out a small contribution of increased drug-induced suicidality associated with venlafaxine.

By combining data on average prescription duration, duration of treatment, and the overall risk of self-harm in patients treated with antidepressants, it is possible to estimate indirectly the public health impact of the observed differences in FTI for venlafaxine versus SSRIs. Taking a possible 2-fold increased baseline risk of suicidality into account, the data suggest that other explanations (i.e. possible toxicity) may account for between 1 in ~330 and 1 in ~500 additional deaths, among those who take <u>any</u> overdose (versus fluoxetine). However, the additional risk may be significantly higher if only 'serious' overdoses are considered (for example. those >2 grams).

Whilst the absolute increased risk can only be estimated, this calculation gives important information on the likely size of toxicity differences, and also suggests that extremely large studies/case series (involving thousands of patients) would be needed to examine the individual toxicities that might account for the observed differences in fatality rates. However, there are very few published studies/case series examining relative overdose toxicity of venlafaxine versus SSRIs, and these have generally been small , and have not been restricted to single-overdose toxicity. The available literature and data from the ADROIT database suggest that venlafaxine *may* be associated with a higher rate of overdose-related seizures, serotonin syndrome and muscle toxicity than SSRIs. The available comparative data do not point towards an increased risk of cardiotoxicity for venlafaxine versus SSRIs, but

are inadequate to exclude such an effect in high-risk groups. Likewise, the data do not suggest that venlafaxine overdose is associated with a higher rate of severe CNS depression than SSRIs. From the available data, it is therefore not possible to deduce the relative importance of the different toxicities, in accounting for venlafaxine's higher FTI.

Amongst the SSRIs, there is some evidence of a relatively higher rate of seizures and possible cardiotoxicity (prolonged QTc interval) for citalopram.

4. Overall conclusion on dose-related toxicity for venlafaxine, and comparisons versus SSRIs and TCA antidepressants

- Venlafaxine can produce a variety of toxic effects in overdose, and is occasionally fatal in doses of ≥2 grams, although the majority of overdoses are non-fatal even at higher doses. Possible mechanisms of fatal toxicity that have been identified include cardiotoxicity, seizures, serotonin syndrome/muscle toxicity and CNS depression, but the relative importance of these mechanisms cannot be assessed from the available data.

- There is considerable variability in individual susceptibility to the various toxicities, and there are no clear explanations for this. However, it seems likely that pharmacodynamic risk factors (such as pre-existing cardiac disease, history of seizure, or presence of alcohol/other factors that might aggravate CNS depression) could increase the risk. Similarly, it is possible that risks may be greater in those with pharmacokinetic risk factors leading to high systemic exposure of venlafaxine, such as CYP2D6 poor-metaboliser genotype (especially when taking potent CYP3A4 inhibitors).

- The data are inadequate to exclude the possibility that drug-induced suicidal behaviour in susceptible individuals may be a factor that contributes towards the overall fatality rate associated with the drug. As there is evidence of an increased risk of suicidality in children, some effect may be present in young adults. However, any effect is likely to be small, and the data are inadequate to compare the relative risk of suicidality between venlafaxine and SSRIs.

- The available evidence suggests that venlafaxine has less potential for fatal toxicity than TCAs, which are widely recognised to be potentially lethal in overdose. Although there are limitations to the data, the evidence suggests that venlafaxine may be associated with a higher rate of fatal overdose toxicity than SSRIs. After taking account of possible prescribing biases leading to an increase in baseline suicidality for venlafaxine users, and after making assumptions on usage and patient behaviour based on published studies, it is *estimated* that this drug may account for between 1 in 330 and 1 in 500 additional overdose deaths (relative to fluoxetine). As this estimate takes *all* overdose behaviour into account (including non-serious overdoses) the additional risk attributable to the more serious venlafaxine overdoses (e.g. >2 grams) versus equivalent large doses of fluoxetine may be significantly higher. However, it should be stressed that these estimations are based on assumptions from a variety of different data sources.

- Analysis of the mechanisms underlying possible differences in the fatal toxicity of venlafaxine versus SSRIs would require large studies and high quality data, neither of which is available. Although some preclinical data suggest that venlafaxine might have a cardiotoxic potential in overdose, and there have been very rare post-marketing reports of cardiac arrhythmia associated with this drug, the limited data from observational data and case-series have not suggested that venlafaxine is more cardiotoxic than SSRIs. Nevertheless, there are insufficient data to exclude an increased risk for venlafaxine in some high-risk cardiac groups. The available literature and UK spontaneous ADR reporting patterns suggest that venlafaxine overdose *may* be associated with more frequent seizures, serotonin syndrome and muscle toxicity than SSRIs, in overdose, however there is no conclusive evidence. It is possible that the observed excess fatal toxicity for venlafaxine versus SSRIs is attributable to very small increases in the risk of a variety of different toxicities.

5. WHAT RISK MINIMISATION MEASURES ARE APPROPRIATE?

In previous regulatory assessments, the observed increased risk of fatal toxicity with venlafaxine has resulted in proposal to restrict

access to the drug to (a) moderate or severe depression and (b) specialist use. Other restrictions have related to cardiovascular contraindications and the need for baseline ECG and electrolyte monitoring. These proposals are discussed alongside others below.

5.1 Restricted use

For anti-depressant users, it is likely that the risk of fatal overdose is highest in the severely depressed, partly because these patients are likely to have access to very large quantities of medicine (because of high daily doses), and partly because they are at greater baseline risk of suicidal behaviour. Assuming that venlafaxine has a greater overdose toxicity than SSRIs, restricting its use to high-risk patients might reduce the burden of fatal toxicity in the majority of less severely depressed patients, provided that the alternative medicine is associated with a lower toxicity (i.e. not a TCA) and has reasonable efficacy. Therefore, restricting venlafaxine solely to use by specialists and/or only for those with moderate/severe depression may have some merits (but it does not guarantee that safer treatment is given to the less severely ill patients). Equally, the severely ill patients may themselves be at greater risk of fatal overdose toxicity if venlafaxine is prescribed in preference to an SSRI. A further consideration is efficacy in the severely ill; venlafaxine has some demonstrated efficacy in severe depression, however the evidence for superior efficacy versus SSRIs in treatment-resistant depression is weak.

There is some evidence that venlafaxine may be associated with higher fatal toxicity than SSRIs, however the data are not conclusive. In light of this, the option of reserving venlafaxine as a second-line treatment (after SSRIs) may be justified in clinical guidance, and this option may be preferable to previous regulatory restrictions as it guides prescribers towards potentially safer medicines.

5.2 Restricted pack size

The Marketing Authorisation (MA) holder has proposed that a restricted pack size (to 2 weeks supply) may be an effective risk minimisation measure, and may be particularly appropriate at time of dose initiation, or titration. Such a measure would reduce the total amount of drug dispensed to the patient and ensure that the patient is reviewed frequently at a time of high risk. Corresponding changes should be introduced to the posology section of the

Summary of Product Characteristics (SPC), cross-referenced to warnings regarding suicidal behaviour and information on overdose.

5.3 Dose

Higher licensed doses may be more efficacious than lower dose, but the risk of side effects, such as hypertension and withdrawal reactions is also higher. Furthermore, a poor-metaboliser might only need to take a relatively small number of daily doses together to reach potentially fatal plasma levels of venlafaxine. It also seems likely that those requiring the highest doses i.e. ≥ 300mg would be severely depressed (having failed to respond to moderate dose titration), may be at an increased risk of suicide and may benefit from alternative treatment strategies. For all of these reasons, it would seem appropriate that such high-doses of venlafaxine are only prescribed under the supervision of specialists.

5.4 Contraindications and warnings relating to specific high dose toxicities

5.4.1 Cardiotoxicity

As it is possible that cardiotoxicity is one of the mechanisms of overdose toxicity, and there is evidence for ventricular arrhythmias in high-risk patients taking the drug, it would be reasonable to contraindicate use in those at very high risk. Warnings would be appropriate in relation to those patients with cardiac disease that *may* increase the risk of arrhythmia. However, it is unlikely that baseline ECG or electrolyte monitoring will be an effective risk minimisation measure, and these recommendations should be removed from product information.

5.4.2 Hypertension

Although hypertension does not appear to be an important issue in relation to overdose fatality, the evidence clearly shows that venlafaxine (especially at higher therapeutic doses) may cause increases in blood pressure that can be severe in some patients. There can be no justification for selecting this antidepressant for patients with uncontrolled hypertension, and this should be contraindicated.

5.4.3 Serotonin syndrome/concomitant SSRIs

The SPC already contains warnings about the possibility of serotonin syndrome, however concomitant SSRI use should be restricted to specialist supervision because of the possible pharmacodynamic and pharmacokinetic interactions, especially in overdose.

5.4.4 Other interactions

As there is considerable heterogeneity in the pharmacokinetic response of poor metabolisers who receive CYP3A4 inhibitors, and as there is relatively little information on the safety implications regarding concomitant use of potent CYP3A4 inhibitors (or drug combinations that inhibit both CYP2D6 and CYP3A4) it would seem appropriate to strengthen the warnings to ensure that these interacting drugs are only prescribed when strictly indicated.

5.5 Overdose section

This section should be modified to include information relating to Fatal Toxicity Index calculations for venlafaxine relative to SSRIs and TCAs, and the limitations of these calculations. This section should emphasise the need for careful monitoring of patients who have taken large overdoses.

5.6 Patient information leaflet

The patient information leaflet for venlafaxine should be modified in line with SPC changes and reviewed for completeness, accuracy and clarity. The inclusion of ‘headline’ information (such as is already present in the Seroxat PIL) may be helpful. Advice for patients with suicidal thoughts to seek urgent medical advice would be important to include in such headlines. The updated PIL should be user-tested.

5.7 Communications

Changes to prescribing advice and product information should be highlighted to prescribers in a letter to healthcare professionals. The MA holder may consider additional communications and educational materials to assist prescribers.

5.8 Conclusion on risk minimisation measures

Concerns regarding the overdose toxicity of venlafaxine have led to previous recommendations to restrict the indication for this drug to moderate/severe depression, for use by specialists only. As a result of the current review, the following risk minimisation measures are proposed in order to reduce exposure in those (possibly) at highest risk of overdose toxicity and provide necessary advice to prescribers and patients.

Regulatory risk-minimisation measures:

- A two-week pack should be introduced and considered for initial therapy, dose changes and all patients who are assessed to be at high risk of suicide.
- Because of the increased risk of therapeutic dose/overdose-related toxicity, and the increased risk of suicidal behaviour in severely depressed patients, initiation of doses ≥300mg should be restricted to specialist care and treatment should be managed under specialist supervision or shared care arrangements.
- Use in those at known very high risk of cardiac arrhythmia and those with uncontrolled hypertension should be contraindicated.
- A warning should be introduced regarding patients with heart disease, which might increase the risk of arrhythmia.
- Concomitant use of SSRIs should only be undertaken on specialist advice.
- Concomitant use of potent CYP3A4 inhibitors (e.g. erythromycin, azoles, protease inhibitors), and drug combinations that inhibit both CYP2D6 and CYP3A4 should only be considered if strictly indicated.
- The patient information leaflet should be updated accordingly, and a headlines section should be introduced, which highlights the advice for patients with suicidal thoughts to seek urgent medical help.
- The new prescribing advice should be communicated in a letter to healthcare professionals.

In addition to these regulatory measures, a further option that may be considered in clinical guidance is for venlafaxine to be reserved as ‘second-line’ treatment after SSRIs.

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