



European Medicines Agency

London, 30 May 2008
EMA/CHMP/266019/2008

CHMP ASSESSMENT REPORT

ON

ANTIDEPRESSANTS

under Article 5(3) of Regulation (EC) No 726/2004

1 BACKGROUND INFORMATION ON THE PROCEDURE

1.1 Article 5(3) of Regulation (EC) No 726/2004

On 26 March 2008, the European Commission presented to the EMEA a request for a CHMP opinion under Article 5(3) of Regulation (EC) No 726/2004 on antidepressants, as a result of a published meta-analysis that questioned the efficacy and clinical relevant effects of antidepressants approved for the treatment of patients with major depression.

2 SCIENTIFIC DISCUSSION

Two recent publications (Kirsch, Deacon et al. 2008; Turner, Matthews et al. 2008) have questioned the efficacy of antidepressants and their place in the therapeutic program for treatment of patients with major depression.

Turner et al. reflected that still more clinical trials with a positive treatment effect are published in peer reviewed journals than studies with a negative outcome and that this may lead to unrealistic estimates of drug efficacy and the apparent benefit-risk estimation. The authors describe that from 74 clinical studies with 12 different antidepressants registered by the FDA, 51% based on FDA-analysis have been considered as trials with a positive outcome and 49% as trials with a negative outcome. However, according to the published literature, they found that 94% of the clinical studies showed a positive outcome. 37 studies considered positive by the FDA have been published and only one positive trial was not published. Studies considered with a negative or failed outcome by the FDA have not been released (22 studies) or published in a way that at least a positive outcome could be presumed by readers (11 studies), only 3 studies considered with a negative outcome have been published as such.

Kirsch et al. performed a meta-analysis on the antidepressant efficacy of four different antidepressants (fluoxetine, nefazodon, paroxetine, venlafaxin) based on their clinical trial files submitted to the FDA. Sertraline and citalopram have not been included as no complete data sets had been available. The authors focused in their meta-analysis (linear and quadratic effects of initial severity on improvement scores for drug and placebo groups and on drug-placebo difference scores) on the primary endpoint in short-term trials (difference between baseline and post-treatment score in the Hamilton-Depression-rating Scale) and used a drug placebo-difference of three points as a criterion for a clinically relevant effect. Based on their analysis they draw the conclusion that drug-placebo differences in antidepressant efficacy increase as a function of baseline severity, but are relatively small even for severely depressed patients. The relationship between initial severity score and antidepressant efficacy was attributed to decreased responsiveness to placebo in the very severely depressed patients, rather than to increased responsiveness to an antidepressant. Given these results, the authors question the clinical relevance of treatment with these four antidepressants and conclude that there is little evidence to prescribe the new-generation of antidepressants, except to the most severely affected patients, unless alternative treatments have been ineffective.

Particularly the publication by Kirsch et al. attracted high interest by the public and media, both studies now are cited with the key message that efficacy of antidepressants may be overestimated and is of questionable clinical relevance. However, the modest effect size of old as well as new generation antidepressants in clinical trials on patients with major depression is well known for many years. The methodological issues of such trials and the large and highly variable placebo response on this particular primary endpoint are taken into consideration by the European Competent Authorities and have led in the past to additional efficacy measures required by EMEA and National Competent Authorities in the approval process of medicinal products for the treatment of major depression. The CHMP was of the opinion that the possible publication bias, a concern in the publication by Kirsch et al., is not an issue in the medicines approval process and, for reasons of transparency, information on all key elements and results of clinical trials submitted to the European regulatory bodies are published in the Public Assessment Report.

As outlined in the “CHMP Note for guidance on clinical investigation of medicinal products in the treatment of depression”, confirmatory trials in patients with major depressive episodes should provide unambiguous evidence of the antidepressant activity and of the effective dose range. The CHMP acknowledged that it is well known that in clinical trials for the treatment of major depression there is high and variable placebo response and therefore, these trials are difficult to interpret (Khan and Brown 2001; Storosum, Elferink et al. 2001; Khan, Detke et al. 2003; Storosum, Elferink et al. 2004; Khan and Schwartz 2005). It is true that in about one-third to two-thirds of the confirmatory planned trials, in which an active standard control is used as a third arm, this standard control is not able to distinguish statistically significant from placebo. Hence, the development program of most antidepressants consists of multiple clinical trials aiming to improve the unavoidable problem of unreliability of studies in patients with major depression.

So the gold standard to establish efficacy of an antidepressant is, according to CHMP, randomized, double blind and placebo-controlled trials, in which robust, consistent and statistically significant results on primary and secondary endpoints can be shown. Improvement in short-term trials must be confirmed as the difference between baseline and post-treatment score in core symptoms of major depression, usually based on validated rating scales, such as the Hamilton-Depression-Rating Scale or the Montgomery-Asberg-Rating Scale. In addition, the clinical relevance of the improvement must be shown in form of proportion of responders or remitters, e.g. 50 % improvement in the validated rating scale for responders or absent or only very mild symptoms of major depression in remission. The cut-off points for these definitions of responders or remitters must be justified and pre-specified in the study protocols. Moreover, a comparison with an established standard treatment product in effective dosage must be shown in at least one three-arm study design and the effects seen in the short-term must be confirmed in a maintenance study in the continuation phase of a major depressive episodes lasting at least 6 months. For this purpose a randomized withdrawal study, also called a relapse prevention study, is the recommended design. This underscores that before a medicinal product is approved by the European regulatory bodies, much more is needed than statistically significant improvements in the primary endpoint in short-term trials based on the well known methodological issues of pivotal studies in patients with major depression.

The result by Kirsch et al. that the drug placebo difference based on changes in the Hamilton-Depression-rating scale between baseline at study entry and end of the short-term treatment period is small, is well known and has been published by different groups using regulatory databases of the FDA or European agencies. In these analyses the relation between initial disease severity and treatment response has been well described, however, with higher disease severity, efficacy of the antidepressant increased and not only placebo effects were smaller. These results based on clinical trials including older antidepressants and new generation antidepressants are in contradiction to the interpretation of Kirsch et al., that this is only based on a lower placebo response.

In a recent meta-analysis based on the entire placebo-controlled documentation for all SSRIs and SNRIs available when these medicinal products were approved at the Swedish Medicines Agency the overall magnitude of effect for the different substances compared to placebo was larger based on the responder rates than with the absolute changes in the Hamilton-Depression rating scale (Melander, Salmonson et al. 2008). With the exception of fluvoxamine, significant differences varying between 13.1% and 19.5 %-units were demonstrated for all SSRIs and SNRIs. Moreover, there was no statistical evidence of a relation between average baseline Ham-D score and difference in percentage of responders.

It can be always discussed whether a difference in responder rates of 16 % is large enough to be considered as clinically relevant. In their analysis of average absolute change from baseline, Kirsch et al. estimate that about 80 % of the drug effect is attributable to placebo. Similarly, with 49 % responders on active treatment and 33 % on placebo it can be argued that two thirds of the drug effect is attributable to placebo. However, the CHMP is of the opinion that such argument is based on the doubtful assumption that the placebo effect and the pharmacological effect are additive. Furthermore, some of the placebo effects are probably due to study specific procedures (increased attention, therapeutic impact of weekly rating sessions) and study design (inclusion and exclusion criteria, outpatients, assessment scales, study duration etc.) that are not present or issues in normal clinical practice (Walsh, Seidman et al. 2002; Khan, Kolts et al. 2004; Khan, Schwartz et al. 2007). Hence, the 16 % difference observed in placebo controlled studies is considered as lower limit of the pharmacological effect that could be expected in clinical practice (Melander, Salmonson et al. 2008).

These results in the short-term trials must be confirmed in clinical trials, in which maintenance of effects is established. Most of these studies follow the above-mentioned randomized withdrawal design and show clearly larger effect sizes for relapse rates between placebo and active treatment with an antidepressant.

Overall, the CHMP was of the opinion that the recent meta-analysis of Kirsch et al. focuses only on one aspect how efficacy of an antidepressant can be estimated and therefore has clear limitations. The authors question the clinical relevance based on an outcome, average absolute change from baseline, which is not an appropriate measure for evaluating clinical relevance. The interpretation presented by the authors is not shared by the CHMP. Contrary to their interpretation, the CHMP concludes that approvals of antidepressants for the treatment of patients with major depression were based on data, which provide robust and sufficient evidence of clinically meaningful benefits in a non-negligible percentage of the patients, and that this benefit is not limited to the most severely depressed patients.

3 OVERALL CONCLUSIONS AND RECOMMENDATIONS

Despite the doubts raised in recent publications on the efficacy and clinical relevant effects of antidepressants, regulatory bodies have established high standards and requirements for the evaluation of antidepressants used for the treatment of major depression, taking into consideration methodological issues in this indication, that allow an adequate risk-benefit assessment in the approval process. Statistically significant (based on improvement in validated rating scales between baseline and study end) and clinically relevant improvements (based on responder rates) must be shown in short-term studies, these short-term results must be confirmed in a randomized withdrawal study establishing maintenance of effects.

Focusing only on statistically significant mean differences versus placebo in change in a rating scale as the Hamilton-Depression-rating scale, as done in the meta-analysis of Kirsch et al., is not an adequate basis for evaluation of clinical relevance and is not sufficient for the approval of an antidepressant.

Overall, the CHMP concluded that the approval of antidepressants for the treatment of patients with major depression are based on data, which provides robust and sufficient evidence of clinically meaningful benefits for patients with major depression.

Therefore, the CHMP is of the opinion that no public health concerns have been identified that are considered as being of Community interest.

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