The European Agency for the Evaluation of Medicinal Products
Evaluation of Medicines for Human Use

London, 12 April 2000
EMEA/CPMP/2775/99

Background to the CPMP Position Paper on Selective Serotonin Uptake Inhibitors (SSRIs) and Dependency/Withdrawal Reactions

The Committee for Proprietary Medicinal Products (CPMP) were asked by the European Commission in a letter dated 16 October 1998 to review the potential for dependency, withdrawal reactions and inappropriate long term use with Selective Serotonin Reuptake Inhibitors (SSRIs), an issue which was raised publicly by Mr Charles Medawar and is under discussion more and more in the public domain. In collaboration with its Safety Working Party (SWP) and its Pharmacovigilance Working Party (PhVWP), the CPMP have examined the available preclinical and clinical data on SSRIs and classical comparators focusing on the dependency and withdrawal aspects of these drugs.

The Safety Working Party (SWP) reviewed the preclinical information. As there is only limited preclinical data in the public domain, the CPMP asked in March 1999 the eight marketing authorisation holders concerned to provide further information for the review. The SWP review of this data was discussed in the CPMP meetings of September and October 1999. Discussions at the level of the Pharmacovigilance Working Party (PhVWP) focused on further evaluation of the clinical evidence related to dependence associated with SSRIs.

On the basis of the recommendations from the SWP and PhVWP, the CPMP drafted a position paper, which was sent to the eight marketing authorisation holders concerned for consultation in December 1999 and in March 2000. Taking into account the comments received, the following position paper was adopted during the CPMP meeting of April 2000.

It should be noted that this position paper is not part of a formal procedure and therefore will not lead to any binding decisions at the level of the European Union. Nevertheless, the CPMP felt that it was important to provide the information available to the public and give an overview of the response to this question.

7 Westferry Circus, Canary Wharf, London, E14 4HB, UK
Tel. (44-20) 74 18 84 00 Fax (44-20) 74 18 86 13
E-mail: mail@emea.eudra.org http://www.eudra.org/emea.html

Preclinical evidence

The Safety Working Party (SWP) review of the preclinical information focused on studies addressing dependency and on studies where withdrawal reactions could be identified. As there is limited preclinical data in the public domain the CPMP asked the marketing authorisation holders of the following products for further information:

Class of products	Generic name	Specific remarks
Classical antidepressants	clomipramine	Comparator as a relatively specific serotonin reuptake inhibitor
	maprotiline	Comparator as a selective noradrenaline reuptake inhibitor
Selective serotonin reuptake inhibitors	fluvoxamine	
	fluoxetine	
	paroxetine	
	sertraline	
	citalopram	
Newer antidepressants	venlafaxine	Serotonin and noradrenaline reuptake inhibitor
	nefazodone	5-HT_2-receptor antagonist, serotonin and noradrenaline reuptake inhibitor

The main observations of the preclinical review are:

- SSRIs are taken as a pharmacological class of compounds. This can be defended on the fact that these compounds were developed on the basis of the "SSRI"-property and the hypothesis that the serotonin reuptake would be of therapeutic relevance. Whether or not it means that properties of individual compounds might be extrapolated to others in the same family is a matter of debate. Where appropriate the review of these compounds should take into account a case-by-case approach.
- Reduced food intake and body weight gain is caused by administration of high doses of SSRIs. It is to be debated whether this is caused by a non-specific toxicological effect or occurs via pharmacological modulation of appetite. Following cessation of dosing, subsequent food intake and body weight gain often surpassed control values. However the data presented in the documentation do not allow a systematic comparison of the compounds, although adequate information on individual compounds was provided.
- Data with respect to self-administration give no support to the hypothesis that SSRIs have strong addictive properties like substances that directly affect the brain reward systems, such as psychostimulants. Some data on self-administration in naive animals has been obtained for fluvoxamine, paroxetine and citalopram only, whereas clomipramine, sertraline and nefazodone have been tested in cocaine-trained animals. Fluvoxamine showed transient self-administration in 1 out of 4 naive animals, whereas sertraline maintained self-administration in only 1 out of 4 cocaine-trained monkeys. On an individual basis and at this early stage of information the compounds can be classified as non-inducing self-administration, although the fact that 2 out of 6 compounds showed marginal effects might be a weak signal.
- Data are published that clomipramine, sertraline and citalopram showed some generalisation in a drug-discrimination procedure in rats to the serotonin-releasers MMAI or MBDB, whereas fluoxetine and paroxetine generalised against ethanol in rats. These are weak signals of rewarding behaviour.
- Some of the SSRIs have been shown to reduce intake of addictive substances like cocaine and ethanol. The interpretation of this aspect is difficult. These findings may point to either a potentiation or a suppression of the "internal" rewarding cue. Some drugs, e.g. paroxetine and fluoxetine, have been shown not to potentiate a stimulant cue (amphetamine and cocaine,

respectively) in a pharmacological way, but for others drugs this aspect did not get sufficient attention.

The main conclusions of the preclinical review are:

- The material provided by the pharmaceutical companies with regard to dependence and withdrawal of SSRIs is of variable quality and quantity. In one or two cases where the studies were considered adequate, responses suggestive of dependency or withdrawal were not obtained. For the majority of the compounds the studies were not designed to study withdrawal phenomena and lack sufficient observations in the critical period after stopping administration.
- Although the available preclinical information does not completely exclude the possibility that SSRIs positively affect the brain reward system, as a class the drugs show no convincing evidence for addictive properties apart from the weak signals noted above in self-administration and discrimination studies.

Clinical evidence

The Pharmacovigilance Working Party (PhVWP) of the CPMP initially considered the issue of withdrawal reactions and possible dependence associated with SSRIs and related antidepressants at the request of the United Kingdom. The PhVWP endorsed the conclusions of the United Kingdom assessment report of April 1998, that:

- The review had not identified evidence that SSRIs were drugs of dependence.
- The product information for all SSRIs should contain appropriate warnings about the well-recognised withdrawal reactions.
- Formal clinical studies to evaluate the nature and extent of withdrawal reactions have not been carried out for all SSRIs.

Following the request of the European Commission that the CPMP should consider this issue, further evaluation of the clinical evidence relating to dependence associated with SSRIs was carried out by France and Germany. No evidence that SSRIs were drugs of dependence was found.

Recommendations

1. The available clinical evidence does not suggest that the SSRIs cause dependence. However the lack of evidence for dependence does not prove the absence of a problem and any evidence, which will emerge or will be produced should continue to be evaluated.

2. For the majority of compounds, evidence from well-designed preclinical studies with respect to dependency and withdrawal was incomplete. Consequently, for these compounds, in the overall assessment of drug safety results from such studies would be a valuable adjunct to ongoing clinical safety monitoring of SSRIs.

3. The key elements of withdrawal reaction statements in the Summaries of Product Characteristics (SPC) should be harmonised throughout European Union and the principles agreed are attached.

4. Further clinical studies may be necessary to better define the frequency and severity of withdrawal reactions with these products, in particular with regard to best conditions of treatment discontinuation.

CPMP Proposal for Principles of SPC Wording on Withdrawal Reactions for SSRIs to be Harmonised Throughout European Union

The following principles for harmonised wording relating to withdrawal reactions in the Summaries of Product Characteristics (SPC) of the Selective Serotonin Reuptake Inhibitors (SSRIs) are recommended by the Committee for Proprietary Medicinal Products (CPMP):

Section 4.8 of the SPC for all SSRIs should include:

1. A statement that although withdrawal reactions may occur on stopping therapy, the available preclinical and clinical evidence does not suggest that SSRIs cause dependence.

2. A list of symptoms reported in association with withdrawal reactions for that product (e.g. dizziness, paraesthesia, headache, nausea and anxiety).

3. A statement that the majority of withdrawal reactions are mild and self-limiting.

4. Advice that prescribers should consider gradual dose reduction when stopping treatment should be included in all SPCs apart from fluoxetine. This statement is not required in the fluoxetine SPC as the long half-lives of fluoxetine and its metabolite mean that the drug effectively tapers itself. (This statement should also appear in Section 4.2 of the SPC.)

General points:

1. The term ‘withdrawal reactions’ should be used, not ‘discontinuation reactions’ as has been proposed by some marketing authorisation holders. It should be made clear that withdrawal reactions by themselves are insufficient to imply dependence.

2. Strong evidence, which would allow definitive statements about the frequency of withdrawal reactions with the different SSRIs, is not available. Any such statements should not be based on the frequency of spontaneous reports, as withdrawal reactions with certain SSRIs are likely to be subject to significant underreporting. Any statements relating to the frequency of withdrawal reactions should be based on the results of clinical trials where these are available.