



The European Agency for the Evaluation of Medicinal Products  
*Pre-authorisation Evaluation of Medicines for Human Use*

London, 25 July 2002  
EMEA/CPMP/600/02/en/Final

**COMMITTEE FOR PROPRIETARY MEDICINAL PRODUCTS (CPMP)**  
**SUMMARY INFORMATION ON REFERRAL OPINION FOLLOWING ARBITRATION**  
**PURSUANT TO ARTICLE 30 OF COUNCIL DIRECTIVE 2001/83/EC FOR**

**Floxyfral and associated names**

International NonProprietary Name (INN): fluvoxamine

**BACKGROUND INFORMATION**

Floxyfral and associated names contains the active substance fluvoxamine, which is an antidepressant. From the registrations in Member States, different Summaries of Product Characteristics have been issued, based on national, divergent decisions. In particular, the therapeutic indications differed significantly. On 26 July 2000, France presented to the EMEA a referral under Article 30 of Directive 2001/83/EC<sup>1</sup>.

The referral procedure started on 27 July 2001 in order to harmonise the Summaries of Product Characteristics (SPC) within the Member States and Norway and Iceland. The CPMP having considered the Rapporteur and the Co-Rapporteur assessment reports, scientific discussion within the Committee and comments from the Marketing Authorisation Holders, was of the opinion that the benefit/risk ratio of fluvoxamine is considered to be favourable for the agreed indications, which are (1) Major depressive episode (2) Obsessive Compulsive Disorder (OCD). The CPMP issued a positive opinion, on 17 January 2002, recommending the harmonisation of the SPC for Floxyfral and associated names. The grounds for referral are appended to this report.

An overall summary of the scientific evaluation is provided together with the amended summary of product characteristics.

A Decision was issued by the European Commission on 30 May 2002.

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<sup>1</sup> Corresponding to Article 11 of Directive 75/319/EEC, for referrals presented before 18 December 2001  
Public

## SCIENTIFIC CONCLUSIONS

### Overall Summary of the Scientific Evaluation of Floxyfral and Associated names

#### - Quality issues

No significant issues relating to Quality were identified.

The pharmaceutical particulars of the SPC were harmonised, except the sections, which need to be introduced nationally by the Member States when implementing the harmonised SPC (sections 6.1, 6.3, 6.4 and 6.5).

#### - Efficacy issues

Fluvoxamine is a Selective Serotonin Re-uptake Inhibitor (SSRI). This compound is indicated for Major Depression and/or Obsessive Compulsive Disorder (OCD). In all EU Member States except two, the indication for use of fluvoxamine is OCD in adults. In three EU Member States, this compound was granted an indication for OCD in children, and in others it was suggested for use in children via the Posology section (4.2).

The submitted dossier demonstrated that fluvoxamine had been tested in the population of patients with a Major depressive episode. In this population short-term efficacy has been shown in the dose range of 100-300 mg/day. The adverse events of fluvoxamine are the ones generally well known for SSRIs (headache, nausea, insomnia, somnolence, dry mouth and others).

Fluvoxamine has been well tested in short-term treatment in the adult population of patients with OCD. In this population short-term efficacy with a modest magnitude of effect has been shown in the dose range of 100-300 mg. However, long-term efficacy has not been shown for fluvoxamine. The adverse events of fluvoxamine are similar to other SSRIs, namely headache, nausea, insomnia, somnolence, dry mouth and others. The dossier submitted by the MAH therefore supports the use of fluvoxamine in adults with OCD. The CPMP recommended that this indication be therefore authorised across all EU member states.

In a 10-week placebo-controlled trial in 120 patients with OCD, aged between 8 and 17 years, a statistically significant improvement was seen in the total population in favour of fluvoxamine at 10 weeks, although the clinical relevance of this effect is small. A further subgroup analysis showed improvement on the clinical rating scale (C-YBOCS) in children whereas no effect was seen in adolescents. The mean dose was 158 mg and 168 mg/day, respectively. The starting dose of 25 mg/day should be increased every 3-4 days in 25 mg increments until an effective dose is achieved. The maximum dose in children should not exceed 200 mg/day.

Taking into account the efficacy shown in the paediatric subpopulation, current medical practices and the current use of fluvoxamine in both children and adolescents there is reason to include dosing information in children and adolescents for this indication in the Posology section of the SPC and data related to the results of a clinical trial in this population has been mentioned in section 5.1 of the SPC.

The pharmacokinetic properties of fluvoxamine are well described in the SPC. Some of the data mentioned are derived from bibliographic sources. Minor changes have been made to the SPC with regard to CYP 2D6 and pharmacokinetics in children.

#### - Safety issues

The majority of adverse events seen with fluvoxamine are common to the class of SSRIs and are often not serious in nature. More serious adverse events, although not frequently reported, should be kept under close monitoring e.g. hypertension, syncope, dyspnoea, flatulence, vertigo, minor increase in creatinine and decreased thrombocyte count. Neuroleptic Malignant Syndrome has been observed and should therefore be included in section 4.4 "Special warnings and precautions" of the harmonised

SPC. In the 10-week placebo-controlled trial in children and adolescents with OCD, frequently reported adverse events with a higher incidence than placebo, were: insomnia, asthenia, agitation, hyperkinesia, somnolence and dyspepsia. Serious adverse events in this study included: agitation and hypomania. Convulsions in children and adolescents have been reported during use outside clinical trials. As controlled data related to long-term treatment of OCD in children and adolescents is lacking, the CPMP considers that further information related to these issues (especially relating to growth, sexual function, educational/cognitive development, and effects on behaviour) should be provided.

Fluvoxamine does not appear to increase the teratogenic risk when used in their recommended doses. Fluvoxamine is excreted in via human milk and therefore should not be used by women who breastfeed.

- Administrative issues

Other sections of the SPC which were not harmonised and which need to be introduced nationally by the Member States when implementing the harmonised SPC are the following: MAH, MA number, date of first authorisation/renewal of authorisation, Date of revision of the text.

### **Benefit/Risk considerations**

Based on the documentation submitted by the MAH and the scientific discussion within the company, the CPMP considered that the benefit/risk ratio of fluvoxamine is favourable in 1) Major depressive episode, 2) Obsessive Compulsive Disorder (OCD), provided that the conditions referred to in Annex IV of the opinion are fulfilled.

## **GROUNDINGS FOR AMENDMENT OF THE SUMMARIES OF PRODUCT CHARACTERISTICS**

Whereas,

- the scope of the referral was the harmonisation of the Summaries of Products Characteristics,
- the Summary of Products Characteristic proposed by the Marketing Authorisation Holders has been assessed based on the documentation submitted and the scientific discussion within the Committee,

the CPMP has recommended the amendment of the Marketing Authorisations for which the Summary of Product Characteristics is set out in Annex III of the opinion and under the conditions set out in Annex IV of the opinion. The major divergences identified at the start of the referral have been resolved, namely, that the indication “Obsessive Compulsive Disorder”(OCD) has been approved in adults, and that the issue of treatment of OCD in children in the paediatric population has been resolved with information added to the Posology Section.

## **ANNEX III**

### **SUMMARY OF PRODUCT CHARACTERISTICS**

**Note: This SPC is the one that was annexed to the Commission Decision concerning this referral for arbitration; the text was valid at that time.**

**It is not subsequently maintained or updated by the EMEA, and therefore may not necessarily represent the current text.**

## 1. NAME OF THE MEDICINAL PRODUCT

Floxyfral and associated names (See Annex II)

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active ingredient: fluvoxamine maleate

Each tablet contains 50 mg or 100 mg of fluvoxamine maleate.

For excipients, see 6.1.

## 3. PHARMACEUTICAL FORM

(See Annex II)

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

- Major depressive episode.
- Obsessive Compulsive Disorder (OCD).

### 4.2 Posology and method of administration

#### *Depression*

The recommended starting dose is 50 or 100 mg, given as a single dose in the evening. It is recommended to increase the dose gradually until an effective dose is reached. The usual effective dose is 100 mg per day and should be adjusted on individual patient response. Doses of up to 300 mg per day have been given. Dosages above 150 mg should be given in divided doses.

In agreement with the consensus statement of the WHO, antidepressant medication should be continued for at least 6 months after recovery from a depressive episode. A dose of 100 mg daily may be sufficient for this use.

#### **Obsessive compulsive disorder**

The recommended starting dose is 50 mg per day for 3 - 4 days. The effective dose usually lies between 100 mg and 300 mg per day. The dosage should be increased gradually until the effective dose is achieved, with a maximum of 300 mg per day for adults.

Doses up to 150 mg can be given as a single dose, preferably in the evening. It is advisable that a total daily dose of more than 150 mg is given in 2 or 3 divided doses.

If a good therapeutic response has been obtained, treatment can be continued at a dosage adjusted on an individual basis. If no improvement is observed within 10 weeks, treatment with fluvoxamine should be reconsidered. While there are no systematic studies to answer the question of how long to continue fluvoxamine treatment, OCD is a chronic condition and it is reasonable to consider continuation beyond 10 weeks in responding patients. Dosage adjustments should be made carefully on an individual patient basis, to maintain the patient at the lowest effective dose. The need for treatment should be reassessed periodically. Some clinicians advocate concomitant behavioural psychotherapy for patients who have done well on pharmacotherapy.

In children over 8 years and adolescents there is limited data on a dose of up to 100 mg b.i.d. for 10 weeks. The starting dose is 25 mg per day. Increase every 3-4 days in 25 mg increments until an effective dose is achieved. The maximum dose in children should not exceed 200 mg/day. (For further details see 5.1)

Patients suffering from hepatic or renal insufficiency should start on a low dose and be carefully monitored.

Fluvoxamine tablets should be swallowed with water and without chewing.

### 4.3 Contraindications

- Trademark tablets are contraindicated in combination with monoamine oxidase inhibitors (MAOIs). Treatment with fluvoxamine can be initiated:
  - two weeks after discontinuation of an irreversible MAOI, or
  - the following day after discontinuation of a reversible MAOI (e.g. moclobemide).

At least one week should elapse between discontinuation of fluvoxamine and initiation of therapy with any MAOI.

- Hypersensitivity to the active substance or to any of the excipients.

### 4.4 Special warnings and special precautions for use

The possibility of a suicide attempt is inherent in patients suffering from depressive episodes and may persist until significant remission occurs. Patients should be carefully monitored.

Patients suffering from hepatic or renal insufficiency should start on a low dose and be carefully monitored.

Treatment with fluvoxamine has rarely been associated with an increase in hepatic enzymes, generally accompanied by clinical symptoms. In such cases treatment should be discontinued.

Glycaemic control may be disturbed, especially in the early stages of treatment. The dosage of anti-diabetic drugs may need to be adjusted.

Although in animal studies fluvoxamine has no pro-convulsive properties, caution is recommended when the drug is administered to patients with a history of convulsive disorders. Fluvoxamine should be avoided in patients with unstable epilepsy and patients with controlled epilepsy should be carefully monitored. Treatment with fluvoxamine should be discontinued if seizures occur or if seizure frequency increases.

On rare occasions development of a serotonin syndrome or neuroleptic malignant syndrome-like events have been reported in association with treatment of fluvoxamine, particularly when given in combination with other serotonergic and/or neuroleptic drugs. As these syndromes may result in potentially life-threatening conditions, treatment with fluvoxamine should be discontinued if such events (characterised by clusters of symptoms such as hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, mental status changes including confusion, irritability, extreme agitation progressing to delirium and coma) occur and supportive symptomatic treatment should be initiated.

As with other SSRIs, hyponatremia has been rarely reported, and appears to be reversible when fluvoxamine is discontinued. Some cases were possibly due to the syndrome of inappropriate antidiuretic hormone secretion. The majority of reports were associated with older patients.

There have been reports of cutaneous bleeding abnormalities such as ecchymoses and purpura with SSRIs. Caution is advised in patients taking SSRIs, particularly in concomitant use with drugs known to affect platelet function (e.g. atypical antipsychotics and phenothiazines, most TCAs, aspirin, NSAIDs) as well as in patients with a history of bleeding or coagulation disorders.

Fluvoxamine should be used with caution in patients with a history of mania/hypomania. Fluvoxamine should be discontinued in any patient entering a manic phase.

When combined with fluvoxamine plasma concentrations of terfenadine, astemizole or cisapride may be increased resulting in an increased risk for QT-prolongation/Torsade de Pointes. Therefore, fluvoxamine should not be co-administered with these drugs.

Due to lack of clinical experience special attention is advised in the situation of post-acute myocardial infarction.

There is limited clinical experience of concomitant administration of fluvoxamine and ECT therefore caution is advisable.

Data in elderly subjects give no indication of clinically significant differences in normal daily dosages compared to younger subjects. However upward dose titration should be done slower in the elderly, and dosing should always be done with caution.

Due to lack of clinical experience the use of fluvoxamine in children for the treatment of depression cannot be recommended.

Long term safety data in children and adolescents especially related to growth, sexual function, cognitive and behavioural development are lacking. Careful monitoring is therefore recommended in this patient population.

#### **4.5 Interaction with other medicinal products and other forms of interaction**

Fluvoxamine should not be used in combination with MAOIs (see also contraindications).

Fluvoxamine is a potent inhibitor of CYP1A2, and to a lesser extent of CYP2C and CYP3A4. Drugs which are largely metabolised via these isoenzymes are eliminated slower and may have higher plasma concentrations when co-administered with Fluvoxamine. This is particularly relevant for drugs with a narrow therapeutic index. Patients should be carefully monitored and, if necessary, dose adjustment of these drugs is recommended.

Fluvoxamine has marginal inhibitory effects on CYP2D6 and seems not to affect non-oxidative metabolism or renal excretion.

##### **CYP1A2**

An increase in previously stable plasma levels of those tricyclic antidepressants (e.g., clomipramine, imipramine, amitriptyline) and neuroleptics (e.g., clozapine, olanzapine) which are largely metabolised through cytochrome P450 1A2 when given together with fluvoxamine, has been reported. A decrease in the dose of these products should be considered if treatment with fluvoxamine is initiated.

Patients co-administered fluvoxamine and CYP1A2 metabolised drugs with a narrow therapeutic index (such as tacrine, theophylline, methadone, mexiletine) should be carefully monitored and, if necessary, dose adjustment of these drugs is recommended.

When given with fluvoxamine, warfarin plasma concentrations were significantly increased and prothrombin times prolonged.

Isolated cases of cardiac toxicity have been reported when fluvoxamine was combined with thioridazine. As plasma concentrations of propranolol are increased in combination with fluvoxamine, the propranolol dose may need to be lowered.

Caffeine plasma levels are likely to be increased during co-administration with fluvoxamine. Thus, patients who consume high quantities of caffeine-containing beverages should lower their intake when fluvoxamine is administered and adverse caffeine effects (like tremor, palpitations, nausea, restlessness, insomnia) are observed.

As plasma concentrations of ropinirol may be increased in combination with Fluvoxamine thus increasing the risk of overdose, surveillance and reduction in the posology of ropinirol during fluvoxamine treatment and after its withdrawal may be required.

##### **CYP2C**

Patients co-administered fluvoxamine and CYP2C metabolised drugs with a narrow therapeutic index (such as phenytoin) should be carefully monitored and, if necessary, dose adjustment of these drugs is recommended.

##### **CYP3A4**

Terfenadine, astemizole, cisapride: see also special warnings and special precautions for use.

Patients co-administered fluvoxamine and CYP3A4 metabolised drugs with a narrow therapeutic index (such as carbamazepine, ciclosporin) should be carefully monitored and, if necessary, dose adjustment of these drugs is recommended.

The plasma levels of oxidatively metabolised benzodiazepines (e.g. triazolam, midazolam, alprazolam, and diazepam) are likely to be increased when co-administered with fluvoxamine. The dosage of these benzodiazepines should be reduced during co-administration with fluvoxamine.

## **Glucuronidation**

Fluvoxamine does not influence plasma concentrations of digoxin.

## **Renal excretion**

Fluvoxamine does not influence plasma concentrations of atenolol.

## Pharmacodynamic interactions

The serotonergic effects of fluvoxamine may be enhanced when used in combination with other serotonergic agents (including triptans, tramadol, SSRIs and St. John's Wort preparations). (see also special warnings and special precautions for use)

Fluvoxamine has been used in combination with lithium in the treatment of severely ill, drug-resistant patients. However, lithium (and possibly also tryptophan) enhances the serotonergic effects of fluvoxamine. The combination should be used with caution in patients with severe, drug-resistant depression.

In patients on oral anticoagulants and fluvoxamine, the risk for haemorrhage may increase and these patients should therefore be closely monitored.

As with other psychotropic drugs patients should be advised to avoid alcohol use while taking fluvoxamine.

## **4.6 Pregnancy and lactation**

Data on a limited number of exposed pregnancies indicate no adverse effects of fluvoxamine on pregnancy. To date, no other relevant epidemiological data are available.

Reproduction studies in animals at high doses revealed no evidence of impaired fertility, reproductive performance or teratogenic effects in the offspring. Caution should be exercised when prescribing to pregnant women.

Isolated cases of withdrawal symptoms in the newborn child have been described after the use of fluvoxamine at the end of pregnancy.

Fluvoxamine is excreted via human milk in small quantities. Therefore, the drug should not be used by women, who breast feed.

## **4.7 Effects on ability to drive and use machines**

Fluvoxamine up to 150 mg has no or negligible influence on the ability to drive and use machines. It showed no effect on psychomotor skills associated with driving and operating machinery in healthy volunteers. However, somnolence has been reported during treatment with fluvoxamine. Therefore, caution is recommended until the individual response to the drug has been determined.

## **4.8 Undesirable effects**

Nausea, sometimes accompanied by vomiting, is the most frequently observed symptom associated with fluvoxamine treatment. This side effect usually diminishes within the first two weeks of treatment. Other adverse events, observed in clinical studies at frequencies listed below, are often associated with the illness and are not necessarily related to treatment.

### *Common (frequency 1-10 %):*

Body: Asthenia, headache, malaise

Cardiovascular: Palpitations/tachycardia

Digestive system: Abdominal pain, anorexia, constipation, diarrhoea, dry mouth, dyspepsia

Nervous system: Agitation, anxiety, dizziness, insomnia, nervousness, somnolence, tremor

Skin: Sweating

### *Uncommon (frequency < 1 %):*

Cardiovascular: (Postural) hypotension

Musculoskeletal: Arthralgia, myalgia  
Nervous system: Ataxia, confusion, extrapyramidal symptoms, hallucinations  
Urogenital: Abnormal (delayed) ejaculation  
Skin: Cutaneous hypersensitivity reactions (incl. rash, pruritis, angioedema)

*Rare (frequency < 0.1 %):*

Digestive system: Liver function abnormality  
Nervous system: Convulsions, mania  
Urogenital: Galactorrhoea  
Skin: Photosensitivity

*Other adverse events observed during marketing*

Weight gain or weight loss have been reported.

Rarely, serotonin syndrome, neuroleptic malignant syndrome-like events, hyponatremia and SIADH have been reported. (see also special warnings and special precautions for use)

It is possible that withdrawal reactions may occur on stopping therapy with fluvoxamine although the available preclinical and clinical evidence does not suggest that this treatment cause dependence. The following symptoms have been reported in association with withdrawal of the product: dizziness, paresthesia, headache, nausea and anxiety. The majority of the withdrawal reactions are mild and self-limiting. When stopping, a gradual dose reduction may be considered.

Haemorrhage: (see also special warnings and special precautions for use)

Very rarely, paresthesia, anorgasmia and taste perversion have been reported.

In one 10-week placebo-controlled trial in children and adolescents with OCD, frequently reported adverse events with a higher incidence than placebo, were: insomnia, asthenia, agitation, hyperkinesia, somnolence and dyspepsia. Serious adverse events in this study included: agitation and hypomania. Convulsions in children and adolescents have been reported during use outside clinical trials.

## **4.9 Overdose**

### *Symptoms*

Symptoms include gastro-intestinal complaints (nausea, vomiting and diarrhoea), somnolence and dizziness. Cardiac events (tachycardia, bradycardia, hypotension), liver function disturbances, convulsions and coma have also been reported.

Fluvoxamine has a wide margin of safety in overdose. Since market introduction, reports of death attributed to overdose of fluvoxamine alone have been extremely rare. The highest documented dose of fluvoxamine ingested by a patient is 12 gram. This patient recovered completely. Occasionally, more serious complications were observed in cases of deliberate overdose of fluvoxamine in combination with other drugs.

### *Treatment*

There is no specific antidote to fluvoxamine. In case of overdose the stomach should be emptied as soon as possible after tablet ingestion and symptomatic treatment should be given. The repeated use of medicinal charcoal, if necessary accompanied by an osmotic laxative, is also recommended. Forced diuresis or dialysis are unlikely to be of benefit.

## **5. PHARMACOLOGICAL PROPERTIES**

### **5.1 Pharmacodynamic properties**

Pharmacotherapeutic group: Antidepressants, Selective serotonin reuptake inhibitors  
ATC code: N06AB08

The mechanism of action of fluvoxamine is thought to be related to selective serotonin re-uptake inhibition in brain neurones. There is minimum interference with noradrenergic processes. Receptor binding studies have demonstrated that fluvoxamine has negligible binding capacity to alpha

adrenergic, beta adrenergic, histaminergic, muscarine cholinergic, dopaminergic or serotonergic receptors.

In a placebo-controlled trial in 120 patients with OCD, aged between 8 and 17 years, a statistically significant improvement was seen in the total population in favour of fluvoxamine at 10 weeks. A further subgroup analysis showed improvement on the C-YBOCS rating scale in children whereas no effect was seen in adolescents. The mean dose was respectively 158 mg and 168 mg/day.

## **5.2 Pharmacokinetic properties**

### Absorption

Fluvoxamine is completely absorbed following oral administration. Maximum plasma concentrations occur within 3-8 hours of dosing. The mean absolute bioavailability is 53%, due to first-pass metabolism.

The pharmacokinetics of Trademark® is not influenced by concomitant food intake.

### Distribution

In vitro plasma protein binding of fluvoxamine is 80%. Volume of distribution in humans is 25 l/kg.

### Metabolism

Fluvoxamine undergoes extensive metabolism in the liver. Although CYP2D6 is in vitro the main isoenzyme involved in fluvoxamine's metabolism, plasma concentrations in poor metabolisers for CYP2D6 are not much higher than those in extensive metabolisers.

The mean plasma half-life is approximately 13-15 hours after a single dose, and slightly longer (17-22 hours) during repeated dosing, when steady-state plasma levels are usually achieved within 10-14 days.

Fluvoxamine undergoes extensive hepatic transformation, mainly via oxidative demethylation, into at least nine metabolites, which are excreted by the kidneys. The two major metabolites showed negligible pharmacological activity. The other metabolites are not expected to be pharmacologically active. Fluvoxamine is a potent inhibitor of CYP1A2 and a moderate inhibitor of CYP2C and CYP3A4, with only marginal inhibitory effects on CYP2D6.

Fluvoxamine displays linear single-dose pharmacokinetics. Steady-state concentrations are higher than calculated from single-dose data, and are disproportionately higher at higher daily doses.

### Special Patients groups

The pharmacokinetics of fluvoxamine is similar in healthy adults, elderly patients, and patients with renal insufficiency. The metabolism of fluvoxamine is impaired in patients with liver disease.

Steady-state plasma concentrations of fluvoxamine were twice as high in children (aged 6-11) as in adolescents (aged 12-17). Plasma concentrations in adolescents are similar to those in adults.

## **5.3 Preclinical safety data**

There is no evidence of carcinogenicity, mutagenicity or impairment of fertility with fluvoxamine.

Reproduction studies in animals at high doses revealed no evidence of impaired fertility, reproductive performance or teratogenic effects in the offspring.

The potential for abuse, tolerance and physical dependence has been studied in a non-human primate model. No evidence of dependency phenomena was found.

## **6. PHARMACEUTICAL PARTICULARS**

### **6.1 List of excipients**

**6.2 Incompatibilities**

Not applicable.

**6.3 Shelf life**

**6.4 Special precautions for storage**

**6.5 Nature and contents of container**

See Annex II.

Not all pack sizes may be marketed.

**6.6 Instructions for use and handling**

No special requirements.

**7. MARKETING AUTHORISATION HOLDER**

See Annex II

**8. MARKETING AUTHORISATION NUMBER**

**9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

**10. DATE OF REVISION OF THE TEXT**