UPDATED SUMMARY MINUTES OF THE COMMITTEE ON SAFETY OF MEDICINES MEETING HELD ON WEDNESDAY 10 MARCH 2004

Committee Members:
Present
Professor G W Duff (Chairman)
Dr M J Donaghy (Co-Vice Chairman)
Professor I V D Weller (Co-Vice Chairman)
Professor A Blenkinsopp
Dr T L Chambers
Professor J K Chipman
Professor J H Darbyshire
Dr J C Forfar
Dr R Leonard
Dr A B Millar
Professor D G Owens
Professor B K Park
Professor M Pirmohamed
Dr P Wilkie

Apologies
Professor J Hunt
Professor D J Jeffries
Professor M J S Langman
Professor J F Smyth
Professor K W Woodhouse
Professor K McPherson
Professor S H Ralston

Members for the day
Professor P Woo
Dr T Rollason
Professor G Buckton (CPS vice Chair)

L M Williams *(Assistant Secretary)*
L Oddotte *(Secretariat)*

Professional Staff of MHRA
Principal Assessors
Dr S Singh - Licensing
Ms S Wark - Pharmacovigilance

Licensing Division
Mr D Brown
Dr P Feldschreiber
Mr R Hemmings

Post-Licensing Division
Dr J Dunne
Dr F Rotblat
Dr J Sisson
Dr N Quarcoo
Dr J Williams

I & E Division
Mr G Matthews

Others
Ms A Ambrose
Ms M Anderson
Mr S Rogers
Professor Sir Alasdair Breckenridge – Chair of the MHRA
Dr J Raine Director of Post Licensing
Dr S Kenyon
Dr R Suvarna
Dr A Eyre-Brook
Dr L Wise
Dr J Woolley
Mr I Meemaduma
Dr T Thomas
Mr J Mean
Dr J Moseley
Mr G Lee
Mr N Goulding
Dr J Nooney
Dr B Grimshaw

Training
Dr E Yousuf
Dr M Udell
Dr E Zouridakis
Dr M Zaman
Dr A Bird

NOTE: MHRA STAFF MAY BE PRESENT FOR ALL OR PART OF THE MEETING OR FOR SPECIFIC ITEMS

1. **<u>Apologies and Announcements</u>**

1.1 The Chairman reminded the Members that the papers and proceedings were confidential and should not be disclosed. Members were also reminded to declare their personal specific, personal non-specific, non-personal specific and non-personal non-specific interests in the agenda items. Members were reminded that they were working to the Final Agenda coloured yellow.

1.1 Apologies have been received by Professors Langman, Hunt, Jeffries, Smyth, McPherson and Woodhouse for the day.

1.2 The Chairman welcomed Professor Patricia Woo and Dr Terence Rollason as members for the day.

1.3 The Chairman welcomed Professor Graham Buckton (vice chair of CPS sub committee) attending as the sub committee's representative following the resignation of David Thurston from the chair of the CPS sub committee and his membership of Committee for personal reasons.

2. **<u>Variation</u>**

The Committee considered twelve (12) applications.

One Member declared a personal non-specific interest and left the room. Two Members declared non-personal non-specific interests but this did not debar them from taking part in the proceedings.

These applications were withdrawn at the date of this review.

[See Note 1 Below]

<u>Paper</u>

3. **<u>Paroxetine – Article 31 referral</u>**

3.1 Dr Leonard declared a personal specific interest and left the room. Drs Donaghy and Forfar declared personal non-specific interests and left the room. Professors Buckton, Chipman, Darbyshire, Park, Pirmohamed, Weller and Dr Millar declared non-personal non-specific interests but this did not debar them from taking part in the proceedings.

3.2 The Committee noted the relevant papers.

3.3 The Committee was reminded that a European referral was initiated by the UK on 12 June 2003 following the receipt of data from clinical trials in children and adolescents showed an increased risk of episodes of self-harm and potentially suicidal behaviour with Seroxat in the

treatment of major depressive disorders in the paediatric population. The Netherlands and UK are acting as lead Member States for this referral. The assessment of the initial submissions from the Marketing Authorisation Holder (MAH) was considered by the CPMP at its meeting in November 2003. Following this discussion at CPMP the MA holder was requested to provide a response to a number of outstanding questions.

3.4 The Committee was informed that its Expert Working Group on the safety of SSRIs considered at its meeting on 27 February 2004 a paper assessing the data submitted by the MA holder in response to these questions.

3.5 The Committee, having considered the data submitted by the MAH, proposed the following recommendations:

1 Suicide/Suicidal ideation
Section 4.4 of the SPC should contain a warning that young adults (<30 years of age) should receive careful monitoring during treatment.

2 Withdrawal reactions
The MAH should be requested to conduct further studies to establish whether the increased incidence of withdrawal reactions in patients treated for anxiety disorders is due to treatment duration, indication or response to therapy.

Sections 4.4 and 4.8 of the SPC should be amended to reflect the available data which suggests that patients treated for anxiety disorders and those treated for a longer duration may potentially be at an increased risk of withdrawal reaction on stopping paroxetine.

3. Risk:Benefit in the paediatric population
The additional analyses performed do not alter the previous conclusions that the balance of risks and benefits in children and adolescents for the treatment of major depressive disorder is negative. Use in this population should remain contra-indicated.

4 Risk: Benefit in the elderly population
The balance of risks and benefits in the elderly population is favourable. However, there concerns were expressed regarding the anticholinergic adverse effects of paroxetine; co-morbidity (hypertension, hypothyroidism) and gastro-intestinal which was not discussed in the MAH's report. It was also commented that elderly patients with dementia may be more likely to develop anticholinergic adverse events although this was not discussed in the MAHs report. The Group considered that these are important areas on which the MAH should be asked to provide further information.

5 Risk:benefit of doses above 20mg

For OCD the recommended dose is 40mg with titration as necessary up to 60mg. No change in the SPC is necessary.

For panic disorder the recommended dose is 40mg. Titration above this dose is not supported by the data. The SPC should be amended accordingly. See below.

For depression, SAD, GAD and PTSD the recommended dose is 20mg. Titration above this dose is not supported by the data. The SPC should be amended accordingly. See below.

The SPCs for the 20mg and 30mg tablet formulations and the oral suspension should be amended as follows:

Section 4.2:
Panic Disorder:
The recommended dose is 40mg. Patients should start on 10mg/day and the dose should be increased weekly in 10mg increments according to the patient's response. Titration above 40mg is not supported by the clinical trial data.

Depression, SAD, GAD and PTSD
The recommended dose is 20mg. Titration above this dose is not supported by the clinical trial data.

3.6 The Committee was informed that based on an analysis of data from a primary care database it was estimated that in 17,100 patients treated with paroxetine for depression a starting dose higher than 20mg was employed.

3.7 In the light of these data suggesting that a significant proportion of patients are started at higher than the recommended dosage and given the likely timescale of the ongoing European referral, the Committee advised that communication reminding health professionals of the recommended dosage in each of the licensed indications, and outlining the lack of clinical trial data to support titration above the recommended dosages, was warranted at this stage. The Committee advised that this communication should be accompanied by a summary of the relevant clinical trial data.

6. Proposals for risk reduction measures and SPC changes

6.1 The MAH should be requested to introduce a scored 10mg tablet formulation.

6.2 Educational material should be prepared for prescribers and patients to ensure that they are fully aware of the need for gradual dose titration.

6.3 A warning about the risk of psychomotor restlessness should be added to section 4.4 of the SPC, together with advice that in the

event of psychomotor restlessness developing it is unhelpful to increase the dose.

6.4 The warnings in the SPC about the risk of withdrawal reactions should reflect:

- the incidence of these reactions
- the data suggesting that they may occur more frequently in association with paroxetine than with other SSRIs, in patients who are treated for anxiety disorder and in patients treated for a longer duration.

4. **Hearings**

The Committee considered two (2) applications as follows:

Application 1: One Member declared a personal specific interest and left the room. One Member declared a non-personal non-specific interest but this did not debar the Member from taking in the proceedings.

This application was withdrawn at the date of this review.

[See Note 1 Below]

Afternoon Session 2pm

Application 2: One Member declared a personal specific interest and left the room. Two Members declared personal non-specific interests and left the room. Six Members declared non-personal non-specific interests but this did not debar them from taking part in the proceedings.

This application was withdrawn at the date of this review.

[See Note 1 Below]

5. **Consideration of the Applications**

Abridged

The Committee considered one (1) application.

One Member declared a personal specific interest and one Member declared a personal non-specific interest and both left the room.

This application was withdrawn at the date of this review.

[See Note 1 Below]

6. **Minutes of the Meeting held on Wednesday 11th February, 2004**

The minutes were agreed and signed by the Chairman as a true and accurate record of the proceedings provided that Dr Donaghy's name is replaced by Professor Pirmohamed in point 7.2.

7. **Matters Arising from the Minutes**

7.1 European Centralised Licensing/Post Licensing Issues – Update/Progress

The Committee noted the oral updates provided by Drs Satish Singh and Frances Rotblat.

8. **Website Minutes of the Meeting held on Wednesday 11th February 2004**

The minutes were agreed for publication provided the amendment at 6 above was made.

Papers

9. **Evaluation of the safety of mirtazapine in children and adolescents aged <18 years – Zispin**

The Committee considered the papers and advised that the license holder should include the following statement (shown in italics) in section 4.2 of the SPC:

4.2 Posology and method of administration

The tablets should be taken orally, if necessary with fluid, and swallowed without chewing.

Adults : Treatment should begin with 15 mg daily. The dosage generally needs to be increased to obtain an optimal clinical response. The effective daily dose is usually between 15 and 45 mg.

Elderly : The recommended dose is the same as that for adults. In elderly patients an increase in dosing should be done under close supervision to elicit a satisfactory and safe response.

Children : Since safety and efficacy of Zispin has not been established in children, it is not recommended to treat children with Zispin. *Two randomised placebo-controlled trials failed to demonstrate efficacy for Zispin in the treatment of children and adolescents with major depressive disorder. Safety*

and efficacy of Zispin in paediatric depression can not be extrapolated from adult data.

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10. **Consultation Letter MLX 300: Review of the Advisory Bodies Structure Laid Down in the medicines Act 1968**

The Committee noted this information.

11. **MLX 301 – Exemptions from Restrictions on Parenteral Administration of Medicines**

The Committee noted this information.

12. **Unlicensed supply of cisapride in the UK**

12.1 The Committee noted that the UK marketing authorisations (MAs) for cisapride had been suspended since July 2000 due to concerns over the cardiotoxicity of cisapride. This followed Committee advice that the

balance of risks and benefits for cisapride was negative in all indications and populations. The Committee also noted that, following an article 31 referral, the European Commission endorsed the CPMP opinion that cisapride-containing products should be authorised within Europe but with restricted indications in adults and children after failure of other treatment options. A condition of the MAs was that all patients treated with cisapride should be enrolled in either a clinical safety study/registry or a clinical trial to evaluate efficacy (DN All this is already in the public domain.)

12.2 The Committee was informed that the MAH (Janssen Cilag) had decided not to implement the Commission Decision in the UK and to cancel the remaining UK licences.

12.3 'The MHRA had received recent notifications for importation of unlicensed cisapride into the UK and the Committee's advice was sought on whether or not the MHRA should object on grounds of safety'.

12.4 The Committee noted that the conditions for safe use of cisapride in the European Commission Decision apply only to active MAs, as defined in the Commission Decision, and that all UK MAs had now been cancelled. The Committee advised that the MHRA should object to importation of cisapride on grounds of safety, both for adult and paediatric use. The Committee agreed that its previous advice relating to cisapride still stands, as set out in the Epinet message of July 2000 and available on the MHRA website.

13. ADROIT (Pharmacovigilance) Statistics

The Committee noted this information.

14. Any Other Business

None.

15. Date and time of Next Meeting

The next meeting will take place on **Thursday 25th March, 2004** at 10.00AM

Note 1: information about these products is being withheld on the grounds that this advice remains confidential as at the date of this summary and publication would be premature while regulatory action continues. The advice will be published in due course. Exemption 10 of the Code of Practice on Access to Government Information applies.