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CHMP ASSESSMENT REPORT

ON

CONVENTIONAL ANTIPSYCHOTICS

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

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1 BACKGROUND INFORMATION ON THE PROCEDURE

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

On 23 October 2008, the United Kingdom (UK) presented to the EMEA a request for a CHMP opinion under Article 5(3) of Regulation (EC) No 726/2004 on conventional antipsychotics. The request resulted from recently available data on the safety of antipsychotic medicines from epidemiological studies especially with regards to the risks of antipsychotics when used in elderly people with dementia.

In 2005, analyses of 17 placebo-controlled studies found that atypical antipsychotics were associated with an increased risk of death when used in elderly people with dementia. The product information for atypical antipsychotics was updated to include warnings about this risk. At that time these warnings did not extend to the older conventional antipsychotics as similar controlled trial data were not available. However, this raised concerns that physicians may switch patients to these drugs based upon the absence of evidence of risk rather than evidence of absence of risk. In response to these concerns, a number of observational studies have since been conducted and published in the medical literature. This report examines these studies, including two large studies based in Canada which suggest that conventional antipsychotics are also associated with an increased risk of death in this population.

Given these new data and in the light of the EU Commission Decision of 7 October 2008 on an Article 30 referral to harmonize the product information for Risperdal/Risperdal Consta and associated names (risperidone) to include the indication for symptomatic treatment of Alzheimer's dementia in particular circumstances and the estimated increase in use of antipsychotics to treat symptoms of agitation, aggression and psychosis in dementia, the UK put forward a request to the CHMP, under Article 5(3) of Regulation (EC) 726/2004, asking the Committee to provide a scientific opinion on the interpretation of the available evidence.

The CHMP opinion was sought on the following:

- (1) the strength of the evidence to suggest that conventional antipsychotics are associated with excess mortality when used in elderly people with dementia;
- (2) the strength of the evidence to suggest that conventional antipsychotics are associated with a greater risk of mortality compared with atypical antipsychotics;
- (3) whether or not the risk can/should be extrapolated to those conventional antipsychotics not included in the studies;
- (4) the need to conduct further studies, including on the possible mechanisms underlying the increase in mortality observed.

1.2 Steps taken for the procedure

During the October 2008 CHMP meeting the following was agreed:

- Dr. Suvarna, UK CHMP alternate Member, was appointed Rapporteur for the review procedure under Article 5 (3) for conventional antipsychotics.
- Prof. Sampaio, Portugal CHMP alternate Member, was appointed Co-Rapporteur for the review procedure under Article 5 (3) for conventional antipsychotics.
- A 30 day-time frame for the procedure was set.
- The procedure started on 23 October 2008.
- The Rapporteur's Joint Assessment Report was circulated to all CHMP members on 14 November 2008.
- On 20 November 2008, the CHMP adopted an opinion.

2 SCIENTIFIC DISCUSSION

2.1 Background

On 7th October 2008, the EU issued its Commission Decision on an Article 30 referral to harmonise the product information for Risperdal/Risperdal Consta and associated names (risperidone) to include an indication for symptomatic treatment of Alzheimer's dementia.

Antipsychotics can be classified by their structure but can also be distinguished by their pharmacology, their action at receptors, and by their clinical properties. Typical (also known as conventional) antipsychotics act primarily at dopamine receptors. Atypical antipsychotics act on other receptors as well as dopamine, and are less likely than typical antipsychotics to cause movement disorders as a side-effect. Both atypical and conventional antipsychotics are associated with an increased risk of cerebrovascular adverse events in elderly people with dementia

Cerebrovascular Adverse Events

In 2004, clinical trial data showed a clear risk of stroke in elderly people with dementia who are treated with the atypical antipsychotics risperidone and olanzapine. At that time there were limited data available for other antipsychotics and it was concluded that the risk of stroke for other antipsychotics could not be excluded, pending the availability of further evidence.

Subsequently in 2005, following completion of further studies, a further review of this issue concluded that an increased risk of stroke in elderly people with dementia could not be excluded for other antipsychotics (atypical and conventional). It was agreed that the product information for all antipsychotics should be updated to include a class warning about this risk.

Excess Mortality

In 2005 an analyses of 17 placebo-controlled trials performed with olanzapine, aripiprazole, risperidone or quetiapine in elderly demented patients with behavioural disorders was published¹. Fifteen of the seventeen trials showed numerical increases in mortality in the drug-treated group compared to the placebo-treated group. An approximately 1.6-1.7 fold increase in mortality was demonstrated in these studies (total study population 5106 patients). The causes of these deaths were mostly due to cardiac events (heart failure and sudden death) or infections (mostly pneumonia).

¹ FDA Public Health Advisory: Deaths with Antipsychotics in Elderly Patients with Behavioral Disturbances, dated April 11, 2005.

The CPMP Pharmacovigilance Working Party also reviewed this issue in 2005. The Summary of Product Characteristics (SPCs) for aripiprazole, olanzapine, paliperidone, and risperidone contain warnings about the risk of increased mortality when these drugs are used in elderly patients with dementia. Risperidone is also associated with an additional increased risk of death when co-prescribed with furosemide in elderly patients with dementia, and this information is also included in the risperidone SPC. The warnings concerning increased mortality did not extend to conventional antipsychotics since there were limited data available at that time. Since then, concern has been growing that physicians may be switching their patients from atypical to conventional antipsychotics in the absence of any evidence of risk (rather than evidence of absence of risk). As a result, a number of observational studies have since been conducted by various research groups in an attempt to determine whether or not the conventional antipsychotics carry a similar risk of increased mortality to the atypical antipsychotics when used to treat elderly people with dementia.

2.2 Recently published literature

2.2.1 Key Published Literature

This report examines the published studies relating to this issue, in particular two recently published observational studies. The literature references for these studies are as follows:

1. Risk of death associated with the use of conventional versus atypical antipsychotic drugs among elderly patients. Schneeweiss et al. *CMAJ*, 176(5): 627-632, 2007
2. Antipsychotic Drug Use and Mortality in Older Adults with Dementia. Gill SS et al. *Ann Intern Med.* 2007; 146: 775-786.

An overview of these papers is provided below.

2.2.1.1 Schneeweiss et al. (2007). “Risk of death associated with the use of conventional versus atypical antipsychotic drugs among elderly patients.” *CAMJ* 176(5): 627-32.

Background

Atypical antipsychotics have been associated with an increased risk of death in elderly people with dementia. The authors of this paper wished to investigate whether this observation also applied to typical (conventional) antipsychotics medications.

Methods

Based in British Columbia (BC), Canada, the authors identified a cohort that was comprised of all residents of BC aged 65 years or more for whom a first prescription for an oral antipsychotic drug had been filled during the period from beginning of 1996 to the end of 2004. The BC Ministry of Health provided physician and hospital administration data that was cross referenced to all prescription drugs dispensed according to the PharmaNet database. Vital status, but not actual cause of death was extracted from the BC Vital Statistics Agency. Patients without an interaction (use and filled a prescription) with the medical services in the two preceding 6 month periods prior to the first use of an oral antipsychotic were excluded. Patients with cancer at study start date were not considered for inclusion. The atypical antipsychotics mainly comprised risperidone, quetiapine and olanzapine, while loxapine, haloperidol, chlorpromazine and trifluoperazine made up the bulk of the oral antipsychotics referred to as conventionals. An extensive list of potential confounders was drawn up recognising that adequate control of “other” predisposing factors that lead to death are critical before one can confidently interpret any difference shown in the analyses. These variables covering socio-demographic characteristics, generic markers of co-morbidity, psychiatric morbidity, prior and current use of anti-cholinergic drugs were used in all the analyses performed. These covered Cox regression, Propensity score analysis and instrumental variable estimation.

Results

The analyses were based on 37,241 patients contrasting 12,882 on conventional and 24,359 on atypical oral antipsychotics. The unadjusted mortality ratio was 1.47 (95% CI 1.39 to 1.56) comparing conventional with atypical. All adjusted analyses provided statistically significantly raised mortality ratios at the 5% level including those restricted within strata, such as dementia status and residence. The propensity score analysis supported these findings. There was also concordance between the estimate of an increase in 3.5 deaths per 100 population in the conventional drug group and that obtained in the instrument variable analysis of an additional 4 deaths for every 100 prescribed a conventional antipsychotic.

2.2.1.2 Gill et al. (2007). “Antipsychotic Drug Use and Mortality in Older Adults with Dementia.” *Ann Intern Med.* 146: 775-786.

Background

The authors of this paper wished to investigate whether antipsychotics were associated with an increased risk of death for patients with dementia and in addition to look at longer term follow up data and differentiate between the non users and the users of atypical and conventional antipsychotics.

Methods

This study used record linkage across 4 administrative health care databases in Ontario, Canada. They identified a cohort of patients with a diagnosis of dementia during the period April 1997 to March 2002 who were 66 years or older. Only new usage of an antipsychotic was taken for a patient to be eligible for inclusion with no differentiation between switching between individual antipsychotics in the same class, as they were assumed to all equally carry the same risk. All cause mortality was taken as the study outcome evaluated at 30, 60, 120, and 180 days after first prescription for an antipsychotic. Stratification of the cohort was used to separately evaluate the data within those living in the community and those living in residential care, recognising the different use of drugs in these two settings. Propensity score analysis was adopted for the analyses of atypical antipsychotics versus non users and atypical versus conventional antipsychotic users, to secure an effective matching. Forty two variables were incorporated into the respective logistic regressions, with additional forced matching on hospitalisation 90 days prior to the index date for a patient because of lack of balance following the earlier procedure. Absolute risk differences in cumulative mortality rates were analysed with bootstrap methods invoked to estimate the 95% confidence intervals. Cox proportional models were then applied to analyse the survival data.

Results

The study had 27,259 matched pairs made up of 9,100 and 4,036 in the atypical antipsychotic versus non use, in the community and long care residents respectively, and 6,888 and 7,235 in the same patient settings for the conventional versus atypical analysis. In the atypical antipsychotic versus no use analysis at 30 days the adjusted hazard ratios were statistically in excess for both the community and long term care patients being 1.31(1.02 to 1.70) and 1.55(1.15 to 2.07) respectively, with associated absolute risk differences of 0.2(-0.3 to 0.6) and 1.2(0.5 to 2.0) respectively. The pattern of excess persisted for the longer follow up periods as well. There was a consistent excess risk for conventional over the atypical antipsychotics for all time intervals analysed with the adjusted hazard ratios and absolute risk differences for community and long term care patients being 1.55(1.19 to 2.02), 1.1(0.5 to 1.8) and 1.26(1.04 to 1.53), 1.1(0.3 to 1.9) respectively at 30 days.

2.2.2 Other Published Literature

A search of the published literature examining the risk of death associated with the conventional antipsychotics in the elderly identified 10 further papers of interest (see section 4). Seven of these papers conclude that conventional antipsychotics are associated with increased mortality when used in elderly patients, whilst three papers conclude that neither atypical nor conventional antipsychotics are associated with increased mortality.

2.3 CHMP Discussion

Both atypical and conventional antipsychotics are associated with an increased risk of cerebrovascular adverse events when used in elderly people with dementia. Additionally, in 2005 atypical antipsychotics were also found to be associated with increased mortality in this population. There were limited data available for conventional antipsychotics at that time and there has been growing concern that physicians may switch patients to conventional antipsychotics based on absence of evidence of risk rather than evidence of absence of risk. A number of groups have since conducted and published observational studies in a bid to determine whether or not conventional antipsychotics, like atypical antipsychotics, are associated with increased mortality when used in elderly people with dementia.

A search of the world-wide literature identified nine studies which suggest that conventional antipsychotics are associated with increased mortality when used in elderly people with dementia. A further three studies which concluded that neither atypical nor conventional antipsychotics are associated with increased mortality in elderly people were also identified (see sections 2.2.1 and 2.2.2 above).

The evidence which suggests that conventional antipsychotics are associated with an increased risk of death in elderly patients with dementia.

The two key studies which suggest that conventional antipsychotics are associated with increased mortality are both large studies (N=37,241 and N= 27,259) and both used record linkage across administrative healthcare databases in Canada.

Schneeweiss et al. compared users of atypical antipsychotics with users of conventional antipsychotics. The unadjusted mortality ratio in this study was 1.47 (95% CI 1.39 to 1.56) comparing conventional with atypical. All adjusted analyses provided statistically significant raised mortality ratios at the 5% level including those restricted within strata, such as dementia and residence. The propensity score analysis supported these findings, although expected given that the logistic regression used to derive the propensity scores, used the same variable as those entered into the Cox regression. There was also concordance between the estimate of an increase in 3.5 deaths per 100 people in the conventional antipsychotic group and that obtained in the instrument variable analysis of an additional 4 deaths for every 100 people prescribed a conventional antipsychotic. The latter result shows a clear dependence on the instrument variable, which was set as the physician's preference for conventional versus atypical antipsychotic.

The authors are well aware of the potential problems in not adequately addressing confounding, misclassifying diagnoses and in particular controlling for confounding by indication. They recognise that there are limitations in the capture of data within their database and note that it is still possible that there was a selective bias in prescribing conventional antipsychotics to those more likely to die.

The consistency of the findings of the analyses within the paper is not proof that they are correct in assigning a causal relationship. They do however, taken together with the other studies, provide support that the analysis of this large dataset suggests that, if not a greater risk, there is little to choose between conventional and atypical antipsychotics when evaluating risk of death within 180 days of commencing treatment. Cause specific mortality data are necessary to investigate the picture within each treatment group to assist in understanding the underlying reasons for this increase.

Gill et al. compared users of atypical antipsychotics to non-users, and users of atypical antipsychotics to users of conventional antipsychotics. In the atypical antipsychotic versus no use analysis at 30 days the adjusted hazard ratios were statistically in excess for both the community and long term care patients being 1.31(1.02 to 1.70) and 1.55(1.15 to 2.07) respectively, with associated absolute risk differences of 0.2(-0.3 to 0.6) and 1.2(0.5 to 2.0) respectively. There was a consistent excess risk for conventional over the atypical antipsychotics for all time intervals analysed with the adjusted hazard ratios and absolute risk differences for community and long term care patients being 1.55(1.19 to 2.02), 1.1(0.5 to 1.8) and 1.26(1.04 to 1.53), 1.1(0.3 to 1.9) respectively at 30 days. Although the sensitivity analyses suggest that the atypical results could be rendered non-statistically significant by the introduction of an unmeasured confounder that is moderately related to mortality, the results of the

conventional antipsychotics would only be influenced by a confounder that is strongly related to mortality.

Propensity analysis, which was suggested in part to have been successful in matching patients for analysis, does not lead to an understanding of which of the 42 variables measured might be important in outcome interpretation. Indeed hospitalisation in the previous 90 days prior to index date in the atypical analysis was forced as a matching variable because of an imbalance in the previous analysis. The sensitivity analysis confirms that, despite a detailed systematic evaluation of the data, there might be other interpretations. As is the case in Schneeweiss et al., alternative interpretations include the prescribing preference of physicians between conventional and atypical antipsychotics dependent on patient setting and dementia severity - which would prevent any reliable conclusions being drawn on whether the excess mortality associated with conventional antipsychotics is greater than that associated with atypical antipsychotics.

The findings of these two studies are supported by other studies included in this report. Further additional findings from the other studies include information on dose relationship and time to onset (Wang et al.), and further information regarding risks associated with individual antipsychotics (Hollis et al. 2006 and Hollis et al. 2007).

The study by Wang et al. is very similar in design to that by Schneeweiss et al., (lead authors are common to both papers). The results of their earlier study (Wang et al.) are consistent with the later study (Schneeweiss et al.) in that conventional antipsychotics were associated with a significantly higher adjusted risk of death than atypical antipsychotics. Wang et al. compared the risk of death within three pre-defined time periods within 180 days. The results showed that the greatest increases in risk occurred soon after therapy was initiated and with higher dosages of conventional antipsychotics. Trifiro et al. also found that the risk of death increased with increasing dose for both antipsychotic types, but found that the risk of death increased with increasing duration of use for atypical antipsychotics.

The two papers published in the Australian and New Zealand Journal of Psychiatry (Hollis et al. 2006 and Hollis et al. 2007) are linked in that one of the studies (Hollis et al. 2007) is an analysis of part of the other larger study (Hollis et al. 2006). The first study showed that the odds ratios (ORs) of death associated with haloperidol, olanzapine, risperidone, pericyazine, thioridazine and chlorpromazine were significant when compared with the reference group (no antipsychotic use in the 120 days prior to study start date) and concluded that haloperidol is associated with significantly higher mortality ratios than other antipsychotic medication. However it is not clear whether this represents drug adverse effects or the medical conditions for which it was dispensed. The subsequent study (Hollis et al. 2007) looked at the risk of death in elderly people in "residential aged care facilities". Olanzapine users formed the reference group. Haloperidol and chlorpromazine were found to be associated with the highest death rates (RR=1.67, 95%CI 1.50-1.84, $p<0.001$ and RR=1.75, 95% CI 1.31-2.34, $p<0.001$ for haloperidol and chlorpromazine respectively). However the authors concluded that despite adjusting for numerous variables the results should be interpreted with caution because confounding by medical illness cannot be excluded.

Many of the methodological limitations encountered are common to all of the studies discussed above. These include: the possibility of unmeasured bias due to unmeasured differences in illness burden - despite attempts to control for this; in many cases the analyses could not control for dose; prescription fills can be an imprecise measure of drug exposure; and other limitations related to the use of registry data. When considered individually as stand alone studies, one of the limitations of these studies is whether or not the results can be generalized to other clinical populations not studied. However, collectively, these studies have shown an increased mortality associated with conventional antipsychotics in patients in the community and those in long-term care homes. Mortality rates were also studied in elderly demented patients hospitalized for pneumonia, and in patients who are presumed to be of lower socioeconomic background.

Relative excess mortality (atypical vs. conventional)

Although the results of a number of these studies suggest that the excess mortality associated with conventional antipsychotics may be greater than that associated with atypical antipsychotics,

methodological limitations mean that these results should be interpreted with caution and no firm conclusions should be drawn.

In general, there is a lack of data in the studies regarding dementia severity and the type of behavioral disorder, and the extent to which these factors determine preferential prescription of antipsychotics for more severe disorders. Propensity-score matching and various sensitivity analyses conducted by Kales et al. attempted to address the issues of patient clinical state and clinician preference for type of medication prescribed. The analysis by Kales et al. used a proxy for severity and suggested that patients with longer standing dementia diagnoses (corresponding to more severe dementia) were more likely to be taking conventional antipsychotics and less likely to be taking other psychiatric medications than patients more recently diagnosed. Also the use of anticholinesterases was lower in patients taking conventional antipsychotics, possibly correlating with dementia severity.

Attempts to adjust for multiple variables were made in a number of the studies discussed above but despite this, it is still possible that there was a selective bias in prescribing conventional antipsychotics to those more likely to die.

Also, Wang et al., who compared users of atypical antipsychotics with users of conventional antipsychotics over 3 time periods within 180 days, found that whilst initially the rate of death for users of conventional antipsychotics was statistically significantly greater than users of atypical antipsychotics, the rates of death began to converge in subsequent time periods.

Causes of death

In the majority of these studies the outcome measured was all-cause mortality. Details on the cause of death are not available and thus a particular cause(s) for the excess mortality observed can not be explored. However, in a number of papers (Schneeweiss et al., Gill et al, and Wang et al.) the authors have reviewed other available literature and highlight several possible mechanisms including sudden cardiac death and QT-prolongation, aspiration pneumonia, venous thromboembolism, cerebrovascular events, and initiating sequences such as falls that would lead to premature death. Schneeweiss et al. who compared users of atypical antipsychotics to a cohort of users of typical antipsychotics, further suggest that anticholinergic properties (affecting blood pressure and heart rate), QT-prolongation, and extrapyramidal symptoms (causing swallowing difficulties) are more common with conventional antipsychotics than with atypical antipsychotics and that these should be further explored as possible explanations for the increased mortality observed in users of conventional antipsychotics vs. users of atypical antipsychotics. However, as discussed above, methodological limitations do not allow a conclusion to be drawn on whether or not conventional antipsychotics are associated with a greater increase in mortality than atypical antipsychotics.

There was one study in which the causes of the deaths were available and analysed. Kales et al. found that the causes of death in their study were not those postulated in the literature cited by Schneeweiss and Gill. Although Kales et al. concluded that both atypical and conventional antipsychotics are associated with increased mortality, their data on the cause of death do not point towards a specific cardiotoxic, vascular or immunological mechanism. Instead they show proportionately more deaths due to dementia-related causes among users of antipsychotic medications and cancer-related causes in users of non-antipsychotic (other psychotropic) medication. Kales et al. commented that the relationship between antipsychotics and mortality is complex and hypothesised that it may be due, in part to a direct influence of antipsychotics on mortality risk but may also reflect remaining confounders from medical and dementia severity such as the pathophysiology underlying neuropsychiatric symptoms that prompt antipsychotic use in dementia. The results of Kales et al. demonstrate that the proportions of patients taking antipsychotics who died from cardiac, cerebrovascular or infectious causes was not different from those taking other psychotropic medication, however the study does not include an untreated cohort.

The evidence to suggest that antipsychotics are not associated with an increased risk of death when used in elderly people with dementia.

Small studies by Raivio et al (N=254), Suh et al. (N=273) and Barak et al. (N=3,111) found that neither atypical antipsychotics nor conventional antipsychotics are associated with increased mortality in the elderly population. However, the study by Barak et al. is not particularly helpful to this assessment given that only 17% of the study population (elderly psychiatric inpatients) was diagnosed with dementia and that all-cause mortality was not studied (outcome measures were restricted to hospitalisation or death due to ischaemic cardiovascular and cerebrovascular events).

Raivio et al. set out to examine the impact of atypical and conventional antipsychotics on mortality and hospital admissions among Finnish elderly institutionalized patients with dementia in a 2-year prospective study and to compare the prognosis with that of non-users. This small study provides data that there is no evidence to suggest that antipsychotics are associated with increased mortality, and the authors go as far as to suggest that antipsychotics may in fact be protective in this particular patient sample, but advised caution in making this interpretation since only the multivariate analyses showed this. The authors indicate that one of the reasons their results conflict with earlier meta-analyses based on randomized controlled trials (for atypical antipsychotics) is that they have included a longer follow-up period, not the 'usual' 10-12 weeks for randomized controlled trials (RCTs).

The authors have conducted a detailed and thorough follow-up of the data at their disposal but, as mentioned above, the study population is small - 254 frail, elderly patients with dementia. Furthermore, the study is based on data collected in the period 1999-2000 when there was little atypical antipsychotic usage. It is also based on patients with an average age of 86-years with one of the main predictors of death in multivariate modelling being age older than 85 years. A major limitation acknowledged by the authors is the assumption that baseline antipsychotic classification/usage holds throughout the follow-up period. There are no data to validate this and withdrawals and initiation of treatment is therefore not known.

The authors thought that by studying a two-year follow-up period they would be able to see whether the increased mortality observed in other studies in the short-term for antipsychotic users would continue for a longer period. However, the mortality pattern observed in this study (i.e. that no increase in mortality rate is seen with the use of antipsychotics versus non-users) is not observed at any time during the 180-day follow-up period reported in the larger studies (Schneeweiss et al. and Gill et al.). This is also at odds with the RCT data for the atypical antipsychotics and the likely more reliable data derived from these large population based studies that report on both "in community" and "in care" environments. The results probably reflect the heterogeneity that will be seen across a multitude of settings where it is not possible to adequately take account of the frailty of the patients receiving treatment.

It is difficult to contrast the smaller studies suggesting no evidence of increased mortality with antipsychotics with the evidence derived from the much larger studies which indicate that both atypical and conventional antipsychotics are associated with increased mortality.

Although the two key studies (Schneeweiss et al. and Gill et al.) are reasonably robust in design and methodology, both have weaknesses and the possibility of residual confounding can not be completely excluded, as discussed above. Similarly, the study by Raivio et al. which concludes that there is no evidence to suggest that antipsychotics are associated with increased mortality has its own strengths and weaknesses. Furthermore, in the majority of studies the cause of death is unknown and cause-specific mortality data are necessary to fully understand the underlying reasons for the increase in risk.

Nevertheless, against this background of uncertainty the results of the two key studies by Schneeweiss et al. and Gill et al. are consistent with the majority of the recently published literature and, on balance the available evidence would seem to point to an increase in the risk of death in elderly people with dementia taking conventional antipsychotics.

Furthermore, these findings should be considered seriously when making clinical recommendations for the care of elderly patients with dementia, especially given ongoing concerns about switching of patients from atypical antipsychotics to conventional following previous warnings about atypical antipsychotics issued in 2005.

3 OVERALL CONCLUSIONS AND RECOMMENDATIONS

In relation to the questions put forward to the CHMP the Committee draws the following conclusions based on the studies discussed in this report.

1. The strength of the evidence to suggest that conventional antipsychotics are associated with excess mortality when used in elderly people with dementia

Conclusion: On balance, despite inevitable limitations of observational data, the available evidence suggests that conventional (typical) antipsychotics are associated with increased mortality when used in elderly people with dementia.

2. The strength of the evidence to suggest that conventional antipsychotics are associated with a greater risk of mortality compared with atypical antipsychotics

Conclusion: Although the results of some of the studies suggest that the excess mortality observed with conventional antipsychotics may be greater than that observed for the newer atypical antipsychotics, this can not be confirmed due to the methodological limitations of the studies.

3. Whether or not the risk can/should be extrapolated to those conventional antipsychotics not included in the studies

Conclusion: No conclusion can be drawn as to whether the risk differs between individual antipsychotics within each class of antipsychotics. It is not safe to assume that the absence of data relating to a particular drug substance equates to an absence of risk for this substance. Until and unless better evidence becomes available, it is reasonable to assume that the increased risk applies to all members of the class.

4. The need to conduct further studies, including on the possible mechanisms underlying the increase in mortality observed.

Conclusion: At present, there is no clear mechanistic basis for the observed increased risk of mortality, and further data would be needed to explore this. Whilst further observational studies could be performed e.g. in national databases such as the UK General Practice Research Database (GPRD), it is unlikely that such studies would be able to provide firm evidence in relation to the underlying mechanisms.

Similarly, existing clinical trial data for conventional anti-psychotics are likely to be too limited to allow a meaningful meta-analysis. It would be possible to conduct large simple randomized trials involving comparator treatment groups in order to better quantify the risk between products, however the results from such trials would not necessarily be generalisable to the rest of the class/classes and it seems unlikely that sponsors will be prepared to conduct such studies. Furthermore, such studies would not provide direct evidence on the mechanism behind the observed increase in mortality. Mechanistic studies may ultimately be needed.

The overall recommendation of the CHMP is therefore that information should be included in the Product Information for all conventional/typical antipsychotics on the increased risk of mortality when used in elderly patients with dementia. The reason for this is, as discussed earlier in this report that the overall weight of evidence, including the reviewed studies, indicates that conventional antipsychotics share the increased risk of death in elderly patients with dementia-related psychosis as has been observed for the atypical antipsychotics.

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Annex 1

Joint Rapporteur's assessment report dated 14 November 2008