Influenza virus resistance to oseltamivir

The Minister's Delegate has asked several questions about the issue of influenza virus resistance with respect to the Medicines Classification Committee (MCC) recommendation to reclassify Tamiflu (oseltamivir) to allow sale by a pharmacist. As Chair of this Committee, I have written this report to further inform the Minister's Delegate about the issue of influenza virus resistance to oseltamivir and to demonstrate that the Committee considered these questions prior to making its recommendation. The MCC considered the application to reclassify oseltamivir at two meetings and specifically sought additional information from the product sponsor before coming to a conclusion. I have presented the key issues relating to viral resistance considered by the Committee in summary form. The Committee has peer-reviewed the data included in this report and confirmed that it is an accurate representation of its considerations and conclusions.

Clinical impact of resistance on infectivity is low

The material considered by the MCC indicated that the issue of viral resistance to the neuraminidase inhibitor group of medicines is quite distinct and different from that seen for bacterial resistance to antibiotics. Unlike antibiotics and the older antivirals, such as amantidine, influenza resistance to neuraminidase inhibitors decreases the biological activity of the virus reducing its infectivity and potentially decreasing the severity and duration of the infection. This loss of "biological competence" occurs as flu virus utilises neuraminidase to infect a cell. Research to date indicates that any mutation that results in loss of neuraminidase activity will decrease the infectivity of the virus and thus the viral load the patient is ultimately exposed to. In some ways mutations decreasing neuraminidase activity produce an effect that echoes the treatment effect of oseltamivir as the primary mode of action of this medicine is to selectively block the neuraminidase receptor on the cell wall preventing the virus from binding to the cell surface and infecting the cell. The evidence therefore supports the contention that you cannot transfer the model of hazard quantification and risk management applicable to bacterial resistance to antibiotics to the neuraminidase inhibitor group of medicines. The submissions from several members of the Pandemic Planning Group, including Lance Jennings, overall concur with this assessment.

Prevalence of resistance is low and stable with increased use

The MCC considered a range of data prevalence of resistance to oseltamivir in various strains of seasonal influenza. The data included published studies and the reports from the World Health Organisation (WHO) and Neuraminidase Inhibitor Susceptibility Network (NISM). The NISM is an expert group charged with specifically monitoring the levels of resistance to oseltamivir from samples of influenza virus collected by monitoring systems around the world. This group produces annual reports and has produced in-depth analysis of the effect of widespread use of oseltamivir in Japan on influenza resistance for each of the past two influenza seasons. The MCC considered material from NISM relating to the over 6 million users of oseltamivir in Japan in the Winter season of 03-04. This report demonstrated a transient increase in the isolation of resistant strains at the end of a treatment period with oseltamivir. The overall rate of resistance being detected in treated patients was 0.3%, compared to 0.38% in earlier clinical trials on smaller cohorts of patients. It should be noted that these findings are based on isolates collected across populations treated, and may underestimate transient resistance developing at the end of treatment. In small scale clinical trials, the rate of detection was higher, with one clinical trial detecting a resistant strain at the end of treatment with oseltamivir in 5.5% of children. The data demonstrates that resistance is more likely to occur if treatment is given at sub-optimal doses, or in the face of a high viral load, i.e. when treatment is delayed. The MCC concluded that as the reclassification proposal is for early intervention in adults, the risks of resistance developing were limited and the consequences on the available evidence were low.

NZ samples included in global resistance monitoring systems

The NZ Influenza Surveillance system administered by ESR during the influenza season collects samples from sentinel practices in NZ for culture and identification. The MCC were informed that the ESR passed these samples on to the WHO collaborating Centre for

Australasia in Melbourne and that the Melbourne centre reports its review of isolates for resistance to the WHO and the NISM network. New Zealand therefore has links into the NISM monitoring system. The NISM data and the expert opinions expressed by this group can inform Medsafe and MCC decision-making about emerging resistance and the need to reconsider reclassification should this be required.

Link between resistance in seasonal influenza strains and pandemic strain unlikely

The data considered by the MCC indicated that the emergence of resistance in a season influenza strain is extremely unlikely to have an impact on whether a future pandemic strain is susceptible to neuraminidase inhibitors. This is not only because oseltamivir–resistant strains of influenza are less biologically competent, but also the strains of seasonal and pandemic influenza are genetically distinct. The H5N1 bird flu appears to be less susceptible to neuraminidase inhibitors not because of a resistance gene but because of other inherent characteristics of that strain. The literature does not support evidence that use of oseltamivir in humans will change the genetic drift in animal species that leads to the emergence of a pandemic strain.

The evidence does suggest that the current H5N1 bird flu strain can develop resistance to oseltamivir and so its ability to prevent morbidity and mortality may be quickly compromised. However this data may be confounded by its use in patients with very high viral loads in whom inadequate doses were administered. A consensus appears to be emerging that you need to use high doses of oseltamivir early in the treatment of patients with bird flu to have any chance to modify the severity of the disease. However the issue of a pandemic strain developing resistance during treatment with oseltamivir is separate from the concern that use of this product in seasonal influenza will in some theoretical way make an as yet unidentified pandemic strain, that may be circulating in birds or animals, more or less likely to be resistant to oseltamivir when it first emerges as a threat to public health. There is no evidence in the submissions, or literature considered by the MCC indicating that resistance to oseltamivir can be transferred from one strain of influenza to another. Given that this exchange would need to occur within a human or animal cell, the presence of resistance in one strain would have an effect on the likelihood of this event occurring. In terms of public access to oseltamivir, if we were really concerned about resistance developing in this manner we would actually be taking steps to stop GPs prescribing the product other than as a treatment for pandemic strains, as the risk of resistance developing is the same irrespective of who initiates treatment.

Reclassification increases overall community supply of oseltamivir

Several submissions from health professionals were keen to encourage use of the product for influenza as there was no doubt the treatment was safe and effective. These submissions argued that increased use would increase manufacturing capacity and so mean more supplies were available “in country” should they be needed for either a seasonal epidemic or a pandemic. These submissions postulated that the health gains from increased use to treat seasonal influenza, in terms of decreased morbidity and mortality, more than compensated for any theoretical risk posed by increased levels of resistance in a seasonal strain. In the Committee’s opinion, this argument has merit as the current evidence suggests that the emergence of resistance in a seasonal strain is more likely to be associated with decreased risk to the individual and any contacts through the loss of biological competence that accompanies mutation to a resistant strain. The Committee felt that the data did not support invoking a “precautionary principle” approach to limit use of oseltamivir in order to increase its usefulness in a pandemic.

Conclusions

The data in the application and submissions on the proposal to reclassify oseltamivir considered by the MCC was deemed to be an acceptable cross-section of the available research by the Committee. The Committee was satisfied that the safety profile for oseltamivir met all of the requirements for reclassification to allow it to be sold by a pharmacist without a doctor’s prescription for the treatment of influenza in adults during the period when influenza was most prevalent. The decision to limit access to this time period was based on the finding that the questionnaire proposed for use by the pharmacist had the

highest positive predictive value for accurately diagnosing influenza during this time period. The Committee considered the issue of the influenza virus developing resistance to oseltamivir during treatment, but concluded that the risk of harm should this occur is small. The Committee acknowledged there was some uncertainty about the issue of the resistance to oseltamivir but were satisfied that there are adequate systems in place, both locally and internationally, to monitor the susceptibility of the virus to treatment such that a decision to reclassify could be taken quickly if new evidence of concern emerged. Lastly the Committee concluded that the advantages of having improved access to oseltamivir for seasonal influenza may have additional benefits in terms of increasing local supply should a pandemic emerge.

The Committee members have reviewed this report and agree that they did consider and review this data, that they support the key points raised, and that it the captures the key evidence