

## INCREASED EMETIC CONTENT FOR PARAQUAT FORMULATIONS

A proposal has been made by ICI Central Toxicology Laboratory to increase the current level of emetic in paraquat formulations by a factor of 5. This would mean that the level of emetic in 'Gramoxone' would be raised from 0.05% to 0.25% w/v of PP796. PSAC\* concluded that, while serious doubts existed as to whether the proposal would result in reduced numbers of human paraquat fatalities, the idea was of sufficient merit to warrant a survey to establish if any benefit would occur in practice.

The reason for the proposal, based on laboratory animal (dog) data, was to ensure that if a minimum lethal dose of paraquat was swallowed (10 ml of 'Gramoxone') then this amount would contain the optimum dose of PP796 (25 mg proposed compared with 5 mg at present) to reliably cause the earliest possible onset of vomiting. The proposal relies on three assumptions:-

- (i) Results from dog experiments will accurately predict effects in man. CTL now have good evidence to show that absorption of paraquat from the gut in dog is similar to man. This assumption may therefore be valid.
- (ii) Man is as sensitive to the effects of PP796 as dog. This assumption may not be true since the previous human evidence, although flimsy, suggests man is significantly more sensitive than dog. Furthermore, human poisoning data tends to support that conclusion.
- (iii) The speed of onset of vomiting is critical in determining the effect of emetic addition on toxicity of paraquat formulations. The validity of this assumption is doubtful. It is well known that the volume of stomach contents prior to vomiting will determine how effective vomiting is in removing stomach contents. In other words rapid vomiting is no good if it only removes, for example, 10% of stomach contents. The CTL dog studies used standardised conditions, involving partially-full stomachs, which do not mimic the range of circumstances applicable in practice.

Hence there exists a substantial degree of uncertainty about the validity of the above assumptions and therefore doubt about the potential benefit of increasing the emetic level.

Furthermore over the past 6 years, the effect of PP796 additions on mortality of paraquat poisoning has been monitored, particularly in the United Kingdom. There is no good evidence to show that this addition has had any effect on paraquat poisoning mortality. Regulatory authorities, whose original expectations about the effectiveness of emetic have not been generally fulfilled, will be naturally sceptical about another proposal concerning the emetic. Therefore in many countries better evidence than we are currently able to provide viz. human data should be made available to support proposals to increase emetic levels. Again this argues that we should undertake further testing before a full-scale launch.

In view of these factors, PSAC recommends that further testing should be done, to assess the effect in human poisoning, before the increased emetic level is introduced on a wide scale basis.

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An important factor for the apparent ineffectiveness of the emetic is that the number of people, who may benefit from the addition, viz. those swallowing between 10 ml and 50 ml 'Gramoxone', are too few in number to enable us to detect any change in mortality. The vast majority of paraquat poisonings are suicides, who swallow larger volumes of Gramoxone (>50 ml) and therefore too much paraquat for the emetic to cope with.

In suicides, since the majority swallow at least 50 ml, they must also swallow at least 5 times the current minimum emetic dose (5 mg). There is no difference in mortality between suicides swallowing emeticised 'Gramoxone' and suicides swallowing 'Gramoxone' without emetic. Therefore increasing the emetic level in 'Gramoxone' by a factor of 5 will not affect outcome in these suicides. It is possible, however, that those swallowing between 10 and 50 ml 'Gramoxone' may benefit from the increased emetic content, but as stated above these people are too few in number to enable us to detect any such benefit.

If a dilute formulation of paraquat containing an increased emetic level is considered, then there may be a chance of seeing a positive effect. Firstly the target range of volume ingested will be increased so that more suicide cases could benefit. For example a 3-fold dilution of 'Gramoxone' would mean that those who may benefit from the increased emetic content, would include patients swallowing between 30 and 150 ml of product. Secondly at doses where the emetic can help, the volume ingested and therefore the volume of stomach contents will be increased, which will optimise the chances of effective vomiting. From this reasoning, PSAC recommends that the effect of increasing the emetic content of paraquat formulations should be tested only in those markets where a dilute formulation (5-12% w/v paraquat ion) is principally available. Japan and France have been identified as potential markets for test survey, but due to confounding factors, particularly in Japan, other countries are being actively considered.

#### Conclusion

In summary, PSAC does not recommend that the increased level of emetic is introduced into paraquat formulations generally. PSAC does recommend that the CTL proposal is investigated on a trial basis in markets where a dilute paraquat formulation is principally sold (5-12% w/v paraquat ion).