

DRAFT - Dog studies Product Safety position document

Product Safety position on the need for acute oral toxicity testing of paraquat formulations in the dog

Following the decision on 22nd June 2010 to replace the US Inteon[®] formulation (A7813K, containing 240 g paraquat ion/litre and 1.5g/litre of the emetic, PP796) as a result of problems in use such as spray nozzle blockage and the formulation gelling in bulk tanks), together with difficulties in the future supply of an appropriate grade of the alginate component of consistent quality, an alternative formulation (A7813Q, also containing 240 g paraquat ion/litre and 1.5g/litre of the same emetic) was developed as a potential direct successor to Inteon[®]. The acute oral toxicity of this new formulation was assessed in the same animal model (the dog) which had been used to evaluate the Inteon[®] formulations developed previously. The rationale for testing was two-fold, firstly we had previously regarded the US 'Inteon' as representing a measurably safer formulation from the perspective of acute oral toxicity than the Gramoxone Max[®] which it replaced (containing 360 g paraquat ion/litre and 0.5 g/litre of the emetic, PP796) and had made external representations, including to US EPA, to that effect. Secondly, we needed to satisfy the US-specific Manufacturing Use Product ("MUP") standard adopted by Syngenta in 2005 which requires that formulations produced from Syngenta paraquat dichloride technical concentrate demonstrably met the toxicological criteria of having an oral median lethal dose ("MLD") of not less than 128 mg paraquat ion/kg bw in the dog.

The basis of our assessment was one of 'safety equivalence', in which the toxicity of the alternative formulation was compared to the toxicity of the Inteon[®] formulation across a range of doses used as proxies for possible human ingestion volumes. The dog was chosen because it appears to be the most appropriate animal model in which the effect of the addition of an emetic (e.g. PP796) can be assessed, because of our extensive background experience with paraquat in this animal model and the need to satisfy the 128 mg/kg bw US MUP criterion.

When tested in the dog, the alternative formulation (A7813Q) satisfied the statistical criteria for assessment of safety equivalence which had been defined prior to animal testing, and was therefore considered to be at least as safe as the Inteon[®] formulation it replaced.

The relevance of this approach to actual human safety has, however, been questioned as a result of a series of clinical monitoring surveys in Sri Lanka and South Korea which ultimately showed no consistent evidence for a significant reduction in mortality arising from oral ingestion of Inteon[®] formulations compared to non-alginate containing formulations, even though the toxicology studies in the dog had suggested otherwise. All animal models have limitations in extrapolating to man. This is particularly so where the endpoint of concern is lethality since in the animal studies there is the obvious need from an animal welfare perspective to intervene, avoiding unnecessary suffering through early termination; while in the human medical environment the imperative is to save the patient through intensive care. The clinical monitoring surveys conducted following the introduction of Inteon[®] technology in South Korea and Sri Lanka do not invalidate the dog as the most appropriate animal model but rather indicate the caution which should be applied in directly extrapolating from the animal model to man.

In addition, specifically in the USA, there has been a historically low incidence of fatalities arising from accidental oral ingestion.. The low frequency of accidental oral ingestions is, at least in part, the result of long-standing voluntary formulation additions (the inclusion of dye, stench and an emetic), prominent labeling ('NEVER PUT INTO FOOD, DRINK OR OTHER CONTAINERS', DO NOT REMOVE CONTENTS EXCEPT FOR IMMEDIATE USE) and on-going product stewardship programs, in combination with the 'RESTRICTED USE' classification of all paraquat-containing formulations (it can only be purchased by a certified applicator who must also apply it or supervise its application).

In addition, we would not normally conduct additional (non-regulatory) acute oral toxicity studies in the dog on new formulations of other active ingredients intended for commercialization in the USA or elsewhere. Animal testing is always to be avoided where possible, particularly so when it would potentially involve testing in a 'higher' species. Therefore on the basis of the results of the non-Inteon[®] formulation (A7813Q) from a Product Safety standpoint with effect from [] we would propose to discontinue tests of the 'safety equivalence' of any new formulations containing paraquat which are intended for commercialization [in the USA] provided they meet the following criteria:

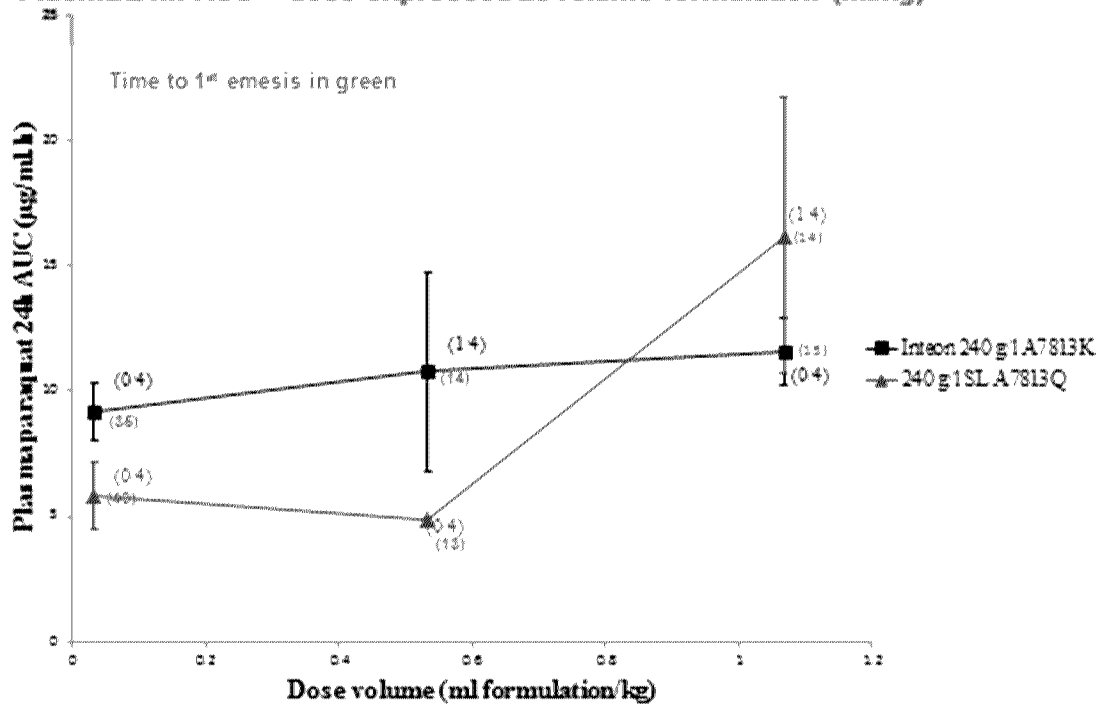
- Paraquat ion content \leq 240 g/litre
- Paraquat ion content $>$ 240 g/litre for commercialization solely through in bulk containers for use in closed transfer systems
- Emetic (PP796) content \geq 1.5 g/litre

The Product Safety studies we conduct to assess acute toxicity will be those routinely required by the US EPA in order to assign the toxicological classification for acute effects. In addition, advice will be given on a case-by-case basis on the likely impact of the addition of any proposed co-formulants.

Appendix 1

Results of evaluation of 'safety equivalence' of 'Gramoxone Inteon' (A7813K) and 'Gramoxone SL' (A7813Q).

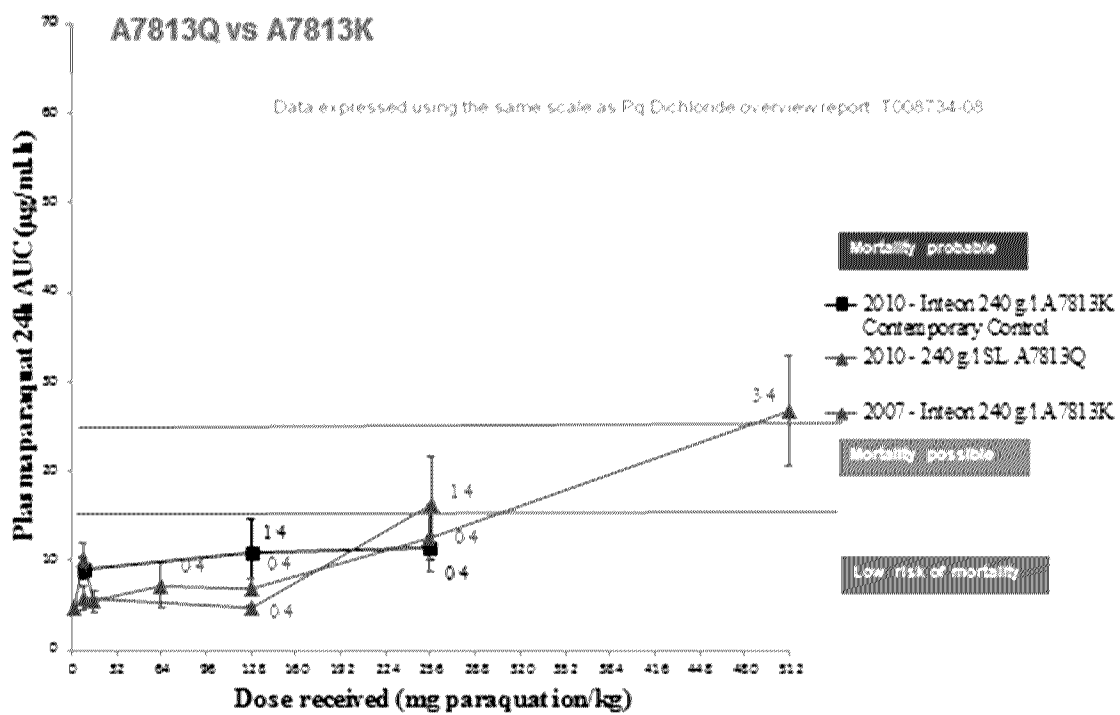
Plasma 24hr AUC – dose expressed as volume formulation (ml/kg)



8 Classification: INTERNAL USE ONLY



A7813Q vs A7813K



9 Classification: INTERNAL USE ONLY

