An update on the assessment of the relative safety of INTEON® and non-INTEON® paraquat formulations

April 2008

Syngenta Crop Protection
Syngenta Intention with the INTEON® Technology

Objective: Developed to eliminate fatalities following accidental ingestion and reduce fatalities from intentional ingestion incidents of paraquat formulations

Based on the inclusion and integrated action of three additional components to paraquat formulations: alginate, increased emetic and purgative.

Hypothesis: Through the combined effect of these three components, INTEON® technology was anticipated to reduce the overall absorption of paraquat.

- The intent of adding the alginate was to form a gel under the acidic conditions of the stomach.
- As a consequence of the gelling, the stomach would react to the increased bulk and delay the transit of paraquat into the small intestine.
- The increased emetic content was designed to invoke more effective vomiting of the stomach contents.
- The addition of purgative was designed to provide faster removal of paraquat that may have reached the small intestine.
Initial Studies with INTEON® and Non-INTEON® (Gramoxone) paraquat formulations: old study design

Formulations Tested
- INTEON® formulation
- Non-INTEON® formulations
  - No emetic
  - With emetic

Study Design
- 3-4 dogs received a series of increasing oral doses of formulation
  - Dogs were re-used – dosed and then rested for one month and then dosed with the next higher dose level
  - All dogs were terminated on day 14-15 of the last dose, or earlier where euthanasia was required for humane reasons.
  - Maximum dose level = 128 mg/kg
  - Key endpoint determined is PQ AUC

Endpoints Measured
- Body weight, food consumption and clinical signs
- 24 hour plasma area under the curve (AUC) data: PQ
- Emesis episodes and vomiting times
- Number of animals requiring euthanasia, pathology of lung and kidney
Understanding of INTEON® Data up to 2007:
Comparison of 24h plasma paraquat AUC levels in dog

Gramoxone 200g/l (no emetic)
(2/3)
(0/3)

Gramoxone 100g/l (1.2 g/l emetic)
(4/4)
(0/3)

US Inteon 240g/l (1.5 g/l emetic)
(1/4)
(0/3)

NOTE: Numbers in parentheses indicate number of animals requiring termination out of three or four tested

mortality probable
mortality possible
low risk of mortalities

mg paraquat ion/kg
24 hour AUC (µg/ml.h)

Gramoxone
Gramoxone emetic 1.2 g/L
Inteon US emetic 1.5 g/L
Scope of new study program

Why did Syngenta conduct additional studies?

To develop a more comprehensive data base across a full range of doses

New studies conducted:

- Two formulations were tested over the full dose response curve
  - US INTEON® formulation (240 g/L containing 1.5g/l emetic)
  - Non-INTEON formulation (Gramoxone Max, 360 g/l containing 0.5 g/l emetic)

- Three formulations were tested but dose range is limited
  - Other non-INTEON® formulation (240 g/l, 0.5 g/l emetic)
  - Other non-INTEON® formulation (200 g/l, 0.5 g/l emetic)
  - Other INTEON® formulation (200 g/L, 1.5 g/l emetic)
Most Recent Studies with INTEON® and non-INTEON® paraquat formulations: new study design

Study Design

- 4 dogs received a single oral dose of formulation
  - Acclimatized four weeks
  - Dosed by gelatine capsules
  - Dogs dosed only once - all dogs were terminated on day 15, or earlier where euthanasia was required for humane reasons
  - Maximum dose set by signs of toxicity
  - Key endpoints are toxicity and plasma PQ

Endpoints Measured

- Body weight, food consumption and clinical signs
- 24 hour Plasma AUC data: PQ and emetic
- Emesis episodes and vomiting times
- Number of animals requiring euthanasia, pathology of lung and kidney
Most recent studies –
US INTEON® (240 g/l PQ; 1.5 g/l emetic)

Plasma Paraquat 24h AUC (μg/ml.h)

Dose received (mg paraquat ion/kg)

NOTE: Numbers in red indicate number of animals requiring termination out of four tested

- US Inteon® (240g/l: emetic 1.5 g/l)

mortality probable
mortality possible
low risk of mortalities
Most recent studies –
US non-INTEON® (360 g/l PQ; 0.5 g/l emetic) formulation

- US Non Inteon® (360 g/l: emetic 0.5 g/l)  
- US Inteon® (240g/l: emetic 1.5 g/l)
Most recent studies – US non-INTEON® (360 g/l PQ; 0.5 g/l emetic) formulation

Plasma Paraquat 24h AUC (µg/ml.h)

Dose received (mg paraquat ion/kg)

- US Non Inteon® (360 g/l: emetic 0.5 g/l) ▲ US Inteon® (240g/l: emetic 1.5 g/l)

mortality probable
mortality possible
low risk of mortalities
Most recent studies –
US non-INTEON® (360 g/l PQ; 0.5 g/l emetic) formulation

- US Non Inteon® (360 g/l: emetic 0.5 g/l)
- US Inteon® (240g/l: emetic 1.5 g/l)
Most recent studies –
US non-INTEON® (360 g/l PQ; 0.5 g/l emetic) formulation

- • US Non Inteon® (360 g/l: emetic 0.5 g/l) 
- ▲ US Inteon® (240g/l: emetic 1.5 g/l)
Most recent studies –
US non-INTEON® (360 g/l PQ; 0.5 g/l emetic) formulation

Plasma Paraquat 24h AUC (µg/ml.h)

Dose received (mg paraquat ion/kg)

- US Non Inteon® (360 g/l: emetic 0.5 g/l)
- US Inteon® (240g/l: emetic 1.5 g/l)

mortality probable
mortality possible
low risk of mortalities
Most recent studies –
US non-INTEON® (360 g/l PQ; 0.5 g/l emetic) formulation

![Graph showing plasma paraquat 24h AUC vs. dose received (mg paraquat ion/kg).](image)

- ▲ - US Inteon® (240g/l: emetic 1.5 g/l)
- ◇ - US Non Inteon® (360 g/l: emetic 0.5 g/l)

- Mortality possible
- Mortality probable
- Low risk of mortalities
Most recent studies –
US non-INTEON® (360 g/l PQ; 0.5 g/l emetic) formulation

- US Non Inteon® (360 g/l: emetic 0.5 g/l)
- US Inteon® (240g/l: emetic 1.5 g/l)
Most recent studies –
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- US Non Inteon® (360 g/l: emetic 0.5 g/l)
- US Inteon® (240g/l: emetic 1.5 g/l)

Dose received (mg paraquat ion/kg)

Plasma Paraquat 24h AUC (µg/ml.h)

Mortality probable
Mortality possible
Low risk of mortalities
Most recent studies –
US non-INTEON® (360 g/l PQ; 0.5 g/l emetic) formulation

Plasma Paraquat 24h AUC (µg/ml.h)

Dose received (mg paraquat ion/kg)

- • US Non Inteon® (360 g/l: emetic 0.5 g/l)  ▲ US Inteon® (240g/l: emetic 1.5 g/l)
Most recent studies

Plasma Paraquat 24h AUC (µg/ml.h)

Dose received (mg paraquat ion/kg)

- • US Non Inteon® (360 g/l: emetic 0.5 g/l)
- ● Representative Non Inteon® (200g/l: emetic 0.5 g/l)
- ▲ US Inteon® (240g/l: emetic 1.5 g/l)
- ● Global Inteon® (200g/l: emetic 1.5 g/l)
- ▲ Non Inteon® (240g/l: emetic 0.5 g/l)
Summary of most recent results

- These studies have provided new insights into the complexity of the factors that influence the absorption of PQ and its lethality.

- There appear to be other factors in these studies that are influencing absorption. The safening effects of the individual components have not been determined.

- Two Gramoxone formulations have been shown to be less toxic in dogs at certain doses than we first assumed so the baseline reference values are different:
  - US non-INTEON® 360 g/l (0.5 g/l emetic) does not show expected response (non-linear dose response)
  - Gramoxone 240 g/l (0.5 g/l emetic) does not show expected response at the two doses tested (the same low toxicity as INTEON® 240 g/l)

- The difference between INTEON® and non-INTEON® formulations is less than the initial dataset indicated.
Sri Lanka Observational Monitoring Survey

Objective
To compare the outcome of human self-poisoning with a standard (non-INTEON®) formulation against a new 200 g/l INTEON® formulation following its introduction into Sri Lanka.

Summary
The survey has shown that INTEON® significantly reduces the mortality of patients following paraquat ingestion.

The overall survival rate is increased from 27.1% to 36.7%, is considered clinically significant, and is consistent with a 2-fold reduction in toxicity (ie 2-fold reduction in PQ absorption)

Published in Peer Reviewed Journal
Conclusions

INTEON® formulations are as safe or safer than non-INTEON® formulations.

The new studies demonstrate there are differences in the dose-response of INTEON® versus non-INTEON® formulations.

- There is a safening through reduction in oral toxicity in the dog with INTEON® compared to the conventional Gramoxone Max (non-INTEON®) formulation

- We have now tested two non-INTEON® formulations at the upper end of the dose range and these are less toxic than expected

- Therefore, the safening effect is not of the magnitude originally estimated

The significance and impact of the new data on future formulation strategy is being evaluated