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EMETIC CONCENTRATION IN PARAQUAT FORMULATIONS

I have reviewed the reports on studies involving the emetic PP796 (ICI 63197) between 1970 and 1986 produced by both ICI Pharmaceuticals and CTL. These studies involved oral dosing of this phosphodiesterase inhibitor in a number of species including man. This data has been previously reviewed in a CTL report (CTL/R/390) in 1976 and it was suggested that a concentration of 0.05% PP796 should be included in paraquat formulations to act as an emetic when lethal doses of paraquat were consumed.

Studies of poisoning cases involving emeticised paraquat formulations have not provided any definitive evidence that the introduction of 0.05% PP796 to paraquat concentrate in 1979 has resulted in a significant reduction in the number of fatalities attributed to the herbicide. This in my view, is not entirely surprising. My conclusion from studying the scientific evidence from clinical studies with the emetic is that the concentration of PP796 recommended in 1976 is probably well below an effective emetic dose in man.

All the animal studies which include dog, pig and primates are in agreement that the minimal effective does of PP796 to induce >50% incidence of vomiting is 0.5mg/kg. Animal studies with PP796 suggest that both the incidence of vomiting and the time to vomit is dose dependent. Clinical studies with the emetic suggested that man was more sensitive than other species to the centrally acting emetic. However data presented to support this is insufficient to be scientifically valid. The potency effect of PP796 is based on one volunteer (out of one) who vomited at an emetic dose of 0.11mg/kg. On a physiological basis there is no reason why man should be more sensitive to emesis. Indeed, data with monkey, dog and pig (all acceptable models of GI function with pharmaceutical submissions to the FDA and CSM) suggest little or no species differences with PP796 to cause emesis.

The original recommendation for the concentration of emetic to be 0.05% was based on "a concentration which would cause vomiting should the minimal potential lethal dose of paraquat formulation be swallowed" (Hart and Whitehead 1984). If 20mg/kg paraquat represents such a minimal lethal dose to man, this would only contain 0.05mg/kg emetic. Thus, ten times this dose would have to be ingested to reach a minimally effective emetic dose of 0.5mg/kg, if there is no species variation.

Cont...

My personal viewpoint, based on scientific judgement of available toxicological data together with the extensive clinical poisoning data, is that the concentration of PP796 should be increased by ten fold from 0.05% to 0.5% in GRAMOXONE. This reduces the PQ: Emetic ratio from 400 to 40. By calculation, I recommend the following levels of emetic to be added to our commercial formulations. This is based on the bipyridyl content: emetic being 40:1.

FORMULATION	Bipyridyl %	Current Emetic %	Recommended Emetic %
GRAMOXONE EXPORT	20	0.05	0.5
GRAMOXONE L	10	0.05	0.25
PREEGLOX	9	0.05	0.23
WEEDOL	5	0.04	0.13

I have summarized the important issues in the attached document, and I would welcome a debate on this suggestion.

Jon R. Heylings

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REVIEW OF THE EMETIC CONCENTRATION IN PARAQUAT FORMULATIONS

CTL EMETIC STUDY CTL/T/2459 1985 (DOG)

0.5mg/kg PP796 is the minimum effective dose in dogs
(0.1mg/kg PP796 had no effect in dogs).

CTL EMETIC/PARAQUAT STUDY CTL/T/2471 1985 (DOG)

0.5mg/kg PP796 is the minimum effective dose to reduce
paraquat toxicity, peak plasma and AUC values (10X).

Dosing solution 0.296% PQ + 0.0074% PP796
PQ: Emetic ratio = 40

PQ Dose = 20mg/kg (lethal)) SURVIVAL
PP796 = 0.5mg/kg (effective))

GRAMOXONE EXPORT (20% PQ + 0.05% PP796)

PQ: Emetic ratio = 400

PQ Dose = 20mg/kg (lethal)) DEATH (IRI STUDY 1987)
PP796 = 0.05mg/kg (ineffective))

Dogs would require a minimum of $10 \times 20 = 200\text{mg/kg}$
PQ to introduce an effective emetic dose. This represents
SEVENTEEN TIMES the LD50 in Dogs.

PREEGLOX (Ex DQ 4.5% PQ + 0.05% PP796)

PQ: Emetic ratio = 90 (Bipyridyl: Emetic ratio = 180)

PQ Dose = 20mg/kg (lethal)	Bipyridyl dose = 20mg/kg (lethal)
PP796 Dose = 0.22mg/kg (ineffective)	PP796 Dose = 0.11mg/kg
DEATH (IRI STUDY)	(ineffective)
	DEATH (IRI STUDY)

CTL EMETIC STUDY CTL/R/391 1976 (DOG/MONKEY)

2mg/kg PP796 used in both species successfully
(proved later to be 4x effective emetic dose).

Dosing solution (Dog) 0.4% PQ + 0.04% PP796

PQ = Emetic ratio = 10

PQ Dose = 20mg/kg (lethal)) SURVIVAL (both species)
PP796 = 2mg/kg (effective))

CTL EMETIC DOSE ESTIMATION IN MAN CTL/R/390 1976

PP796

<u>mg</u>	<u>mg/kg</u>	<u>n</u>	<u>No vomiting</u>	<u>%</u>
0.25	0.0035	1	-	-
0.5	0.007	1	-	-
1	0.015	2	0/2	0
2	0.03	3 + 34	4/37	11
3*	0.04	2	-	- * Carried out but not
4	0.06	2	1/2	50 stated in report.
8	0.11	1	1/1	100 (<- What if 0/1?)

EVIDENCE FOR MAN BEING MORE SENSITIVE TO PP796

SCIENTIFIC ARGUMENT

- (i) Dose Response Data - Insufficient evidence based on one volunteer at 0.1mg/kg.
- Not statistically proven
 - No evidence of D/R in man
 - Even if present data was proven it makes man only 5x more sensitive not 10x.
 - Doses below 0.5mg/kg are not dose related in animals.
- (ii) Delay in Absorption by tablet compared to solution - Possibly by a few minutes but unlikely to affect outcome .
- Lipophilic compound.
 - Adding solid PP796 to a capsule caused vomiting within 15 min in dogs.
- (iv) Synergism between emetic and PQ inducing vomiting - Constant factor between species if important.
- PQ vomiting effect occurs after peak plasma values therefore of no use.
 - CTL studies proved that 0.5mg/kg required with 20mg/kg PQ.
- (v) Species variability - No physiological basis with centrally acting emetics.
- Pig, Dog, Monkey all respond only at 0.5mg/kg
No reason why unsuspecting humans should respond at a lower dose.

GENERAL POINTS IN CTL/R/390 REPORT CONCLUSION

Principal Reasons for 5mg PP796 in 10ml (0.05%) being recommended in 1976.

- (i) "Irritant nature of formulation - No rationale for this at all.
would enhance vomiting response" PQ induced vomiting takes several hours. Time to vomiting is central to the argument.
- (ii) "Soluble dispersed form is more - Not proven and extremely unlikely
bioavailable than solid" with this compound. Solid PP796 causes vomiting in minutes in dogs.

The 1976 argument was based on people consuming several lethal doses. Even if this data was proven valid, suicides involving 1-2 lethal doses would not vomit - nor would the ACCIDENTAL poisonings.

PROBLEMS ASSOCIATED WITH INCREASING EMETIC CONCENTRATION
FROM 0.05% to 0.5% IN AQUEOUS PARAQUAT CONCENTRATES

- SIDE EFFECTS? Emesis is the chief side effect in man.
PP796 would not have achieved development status if there had been serious toxicity problems.
Dogs can tolerate 20mg/kg PP796. There were no treatment related bodyweight changes. Food consumption was 100% in all dogs at all times. Vomiting occurred within 10 min but had ceased by one hour. Dogs had fully recovered by 2-3 hours. This 20mg/kg dose of PP796 represents 400 times the effective emetic dose.
- COST? Manufacturing costs may double but the Emulsion programme can bear a penalty of £1000 per tonne.
There would be no formulation, spray, herbicidal or development problems.
- REGISTRATION? Level of PP796 in WEEDOL was doubled in 1985 from 0.02 to 0.04%. There are no registration difficulties below 5% additive concentrations.
- SOLUBILITY? PP796 is poorly soluble in water. However, an aqueous solution of 1% can be made (CTL/T/2459). Therefore, GRAMOXONE with 0.5% should be feasible.

RESULT OF INCREASING EMETIC CONCENTRATION FROM 0.05% TO 0.5%
IN AQUEOUS PQ CONCENTRATES

1. Reduce the number of fatalities attributed to paraquat poisoning (especially accidentals and homicides).
2. Protect registration in established territories.
3. Open up new markets on the basis of improved safety.
4. Move back ultimately to higher strength concentrates.