Richmond, California
August 25, 1976

CLASSIFIED

PARAQUAT FORMULATIONS
File No. 721.5PQ
105.3 Paraquat Technical-Treatment

D. B. BARLOW:

Attached is the information received from PPD regarding the emetic formulation of paraquat. This will be a topic for discussion at our September meetings in the United Kingdom, i.e. toxicology, residues, metabolism, efficacy, timing/nature of our submission to EPA, etc.

A key question requiring resolution is: Should ORTHO plan and conduct an expedited registration program? I request your comments. By copy of this memo, I also seek comments and advice from E. L. Stripling, Jr.

Note that Braunholtz has requested that this information be handled as highly confidential.

J. N. OSPENSON

LRS:mrr

cc: H. G. Franke
B. F. Quisenberry + attachment
E. L. Stripling, Jr. + attachment
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Your ref | Our ref JTB/DMG | Date 4 August 1976

Dear Nils

New Paraquat Formulations

I am sending you as promised, copy of our draft internal statement summarising the present position on the emetic formulation of paraquat. With your assurance that this could be handled within Chevron as highly confidential material, we may have included detailed information that is of background value rather than immediate importance to you, but this may help to suggest areas for further discussion that you would like to raise in our September meetings.

You will note that a letter has been sent to our Pesticide Safety Precautions Scheme (PSPS); we feel confident that within the next few days we will receive their approval to the limited operator hazard study to which reference is made in the attached report.

You will also see that if these trials do not show up any problems we now aim to apply for provisional or limited commercial clearance at the end of October 1976, so that sales could begin at least in the UK in the spring of 1977. Please do not hesitate to let me know if you have specific questions arising from the enclosed data.

You will by now have had my telex referring to proposal to change our meeting dates back to September 8, 9 and 10. Looking forward to seeing you then.

With kind regards,

Yours sincerely,

J T Braunholtz

PP. 796. Status Summary July 1976

PP. 796 was developed by the Pharmaceuticals Division of ICI Ltd. between 1968 and 1972 as a potential drug for the relief of asthma. Toxicological studies were undertaken (for summary see Appendix 1) on the satisfactory outcome of which a Clinical Trials Certificate was granted by the Committee for the Safety of Medicines. On the basis of this Certificate human trials were undertaken in five centres in the U.K. involving 29 personnel. It became clear from these trials and from data being simultaneously generated in monkeys that PP. 796 was an effective and reliable emetic agent of considerable potency. For this reason the development of the compound as a therapeutic agent was abandoned.

In January of 1976 the possibility of incorporating PP. 796 in Gramoxone was identified. Subsequently a programme has been pursued to establish whether the predicted usage of PP. 796 for improving the safety of Gramoxone can be realised. Such realisation is dependant upon the fulfilment of a number of criteria which are outlined below. The time course of our activities is presented in the attached network (Appendix 2).

Formulation

The level of inclusion of PP. 796 in Gramoxone has, after careful consideration of human data, been established as 0.05% w.v. This will give a dose of 5 mg in 10 ml of Gramoxone which is likely to produce emesis within 15 minutes in 80% of those ingesting such a quantity.

It is now clear that it will be possible to formulate PP. 796 in Gramoxone S Gramoxone UK and Gramoxone Export. Stability information to date indicates no physical or chemical problems. The material which has been used in tests so far has been of pure pharmaceutical grade and consideration is

being given to checking the stability produced from a formulation made up from PP. 796 of 90% purity. In addition, in order to give satisfactory patent coverage, formulations containing the emetic agent at much higher concentrations will be examined from the stability aspect.

Metabolism and Environmental work

Radiolabelled PP 796 will be available by the end of July, it is planned that this material will be used to examine the fate of the compound in plants, water and soil. It is not possible at this stage to accurately predict the likely fate of this compound in the foregoing environments; it is clearly necessary to obtain this information as soon as possible. A method for the analysis of the compound will be available by August; it is intended that residue samples be taken from current and forthcoming trials which, in combination with the information from metabolism studies, will give an indication of the environmental stability of this compound. A combination of a reasonable amount of degradation, coupled with the extremely low rate of application during spraying may indicate that it will not be necessary to embark on extensive cattle palatability or animal transfer studies. At the present time it is not intended to embark upon soil leaching studies, these can however be put on at short notice if it is felt necessary to do so.

Process Chemistry

Pharmaceuticals Division are currently investigating the process development required to produce tonnage quantities of PP. 796. They are confident in their ability to supply forthcoming requirements for the compound.

Patents

Our present current patent strategy, which is both comprehensive and intensive, is to cover as many territories in the world as possible, both

for PP. 796 itself and for compounds in other chemical classes which could be deemed to have emetic potential.

Herbicidal Activity

Results from metre box trials which have been undertaken this Spring all clearly demonstrate that the presence of the emetic agent has no effect at all on the efficacy of paraquat.

Biological Efficacy

Work has recently been done at CTL in rats, dogs and monkeys to demonstrate that the presence of the emetic agent is capable of reducing the fatalities likely to ensue from swallowing paraquat solutions. The evidence to date, which has yet to be fully completed, is extremely encouraging, in that groups of dogs and monkeys, when receiving fatal quantities of paraquat in the presence of the emetic agent, were seen to survive. The information from rat studies, a species which does not vomit, indicates that there is possibly a reduction in gastric emptying produced by PP 796. CTL will do further work to qualify these initial findings.

Registration

A letter has been sent to PSPS, outlining the emetic concept. It is hoped that the PSPS will operate a quick review of this data, thereby giving us trials clearance for the early Autumn. This trials clearance will permit us to study in greater depth the possible hazard, in terms of side effects of nausea, which could ensue from the large scale spraying of an emetic formulation. A proposed protocol for such studies has been produced. On theoretical grounds there is no reason to believe that operators will suffer from any effects from the use of this compound, however it is clearly felt important that this aspect of formulation be examined to our full satisfaction. This information will form part of the second phase of our

registration strategy which is application for Provisional Commercial Clearance to be submitted at the end of October this year, this submission will include the toxicology information, environmental aspects, formulation stability, herbicidal effects together with information on residues and possible taint. The latter is being examined at Chipping Camden using material from potato trials.

It is proposed that consideration be given to presenting the emetic formulation concept to other registration authorities, in particular the EPA, as soon as it is politic to do so.

Summary

On the basis of evidence to date there is every reason to be optimistic in the realisation of a reduction of fatalities by means of an emetic formulation containing PP. 796. It is our current view that, by September of this year we will have sufficient data to consider the extension of such a formulation to all territories following the UK introduction in February 1977.

DMF 7/76

APPENDIX I

SUMMARY OF THE TOXICITY OF PP796

(2-amino-6-methyl-5-oxo-4-n-propyl-4,5-dihydro-s-triazolo-[1,5-a]pyrimidine)

Acute Toxicity

acute	oral	LD50	mouse	300-310mg/kg
acute	oral	LD50	rat	150-155mg/kg
acute	iv	LD50	mouse	150mg/kg
acute	iv	LD50	rat (female)	50-60mg/kg
acute	iv	LD50	rat (male)	60-75mg/kg

In rabbits 5mg/kg intravenously killed one out of two rabbits, 20mg/kg killed two out of two rabbits.

The mice that died after oral administration had convulsions and died within minutes of dosing with the exception of a few animals which died from general inanition two to four days later. Rapid respiration was seen immediately after the oral dosing of rats with the compound. All the animals which died did so from general inanition within 48 hours of dosing except for one animal which died after 3 days.

Animals receiving intravenous doses developed a rapid respiration. The majority of mice receiving 100 and 150mg/kg had convulsions within an hour after dosing but many recovered. The mice that died did so within fifteen minutes of dosing. The rats receiving an iv dose salivated profusely within a few minutes of dosing. All the rats which died, except for one, died within the first twenty-four hours.

No gross abnormalities were seen at autopsy

Skin Irritation

PP796 cream and PP796 ointment were applied to intact, shaved skin of six albino rabbits twice daily for ten consecutive days. Slight to moderate erythema and desquamation were observed with the cream applications and slight erythema with the ointment.

Similar applications of the cream to abraded skin caused slight to mild erythema and desquamation, while the ointment caused only slight erythema.

Neither of these preparations caused sensitisation in the rabbit.

Emetic Effects

The maximum tolerated non-emetic dose of PP796 in monkeys and marmosets appears to be in the range of 0.1 to 0.5mg/kg.

Short-term Toxicity

Two groups of rats were given PP796 by mouth in doses of 5mg/kg and 1.5mg/kg daily for 18 days. There were no changes attributable to the administration of PP796.

Two dogs were given daily increasing oral doses of PP796 from 0.1mg/kg to 1.5mg/kg over 39 days. The female vomited approximately 2½ hours after dosing at 0.5mg/kg on the 5th day and was slightly ataxic after a dose of 0.6mg/kg four days later. The male vomited on several occasions, after the twenty-first dose (1.3mg/kg), the twenty-eighth dose (1.5mg/kg) and after feeding on the 29th day. No histological changes were observed in either of the animals.

Subacute Toxicity

Three groups of rats were fed 0.25, 1.25 and 5mg/kg PP796 daily for three months. At the end of the three month period five male and five female rats from the higher dosage group remained undosed for twelve weeks to assess the reversibility of any lesions.

No abnormalities attributable to the compound were found in the rats in the highest dosage group on haematological and histological examination.

On biochemical examination of the high dose level rats, no abnormalities were observed in the levels of SGOT, ICDH or total protein. Slightly elevated levels of alkaline phosphatase were found in both the male and female treated rats on day 21, on day 35 the levels were significantly different from controls but by day 84, had returned to the normal range. Significantly elevated levels of urea were present in female rats on day 35 and in all five tested females after 84 days. Male rats also showed a slight elevation of serum urea levels on day 35 but not on day 84. The kidneys of the treated rats were normal. There were no significant differences between organ weights in treated and control rats.

There were no histological changes attributable to PP796 in rats left for twelve weeks to assess the reversibility of any lesions.

Three groups of dogs were fed 0.15, 0.5 and 1.5mg/kg PP796 daily for 3 months. One male and one female from the top dose group remained undosed for six weeks after the dosing period to assess the reversibility of any lesions.

Vomiting occurred sporadically in six of the animals in the highest dose groups and three in the middle dose group from the ninth day onwards.

No abnormalities attributable to the compound were found in the dogs on haematological, biochemical and histological examination and there were no effects on blood pressure, heart and respiration rate, ECG or organ weights.

No changes attributable to PP796 were found in the dogs tested for reversibility of any lesions.

Teratogenicity

Female proven rabbits were dosed orally with 0.25, 0.75 and 1.25mg/kg PP796 on days 6-18 of pregnancy, and female rats were fed 0.25 and 1.25mg/kg PP796 on days 6-15 of pregnancy inclusive.

At 1.25mg/kg PP796 showed signs of maternal toxicity in both rats and rabbits ie lack of appetite, poor maternal weight gain and (in rabbits) two spontaneous abortions. In rabbits 0.75mg/kg and 1.25mg/kg also caused an increase in resorptions although this was not observed in rats.

In rats and rabbits PP796 has no teratogenic effects at doses used and has little significant effect on pregnancy, littering or weaning.

Mode of Action

PP796 is a phosphodiesterase inhibitor. It increases the resting levels of cyclic AMP in the guinea pig lung and kidney.

In tests with perfused isolated guinea pig lung PP796 at a concentration of 5ug/ml inhibited almost completely the histamine released following injection of antigen. At lower doses the effect was extremely variable.

PP796 is active against bronchospasm induced by a large dose of histamine.

Metabolism

C^{14} PP796 has been dosed po to rat, mouse, guinea pig, beagle and rhesus monkey. The greater part of the radioactivity is excreted rapidly in the urine. A rhesus monkey vomited within 3 hours of receiving 0.08mg/kg; the vomit contained 42% of the dose, of which at least 93% appeared to be unchanged 63197. Monkey rat and guinea pig produce one major metabolite common to all three species.

The half-life of PP796 in man was between 1½ and 3½ hours.

Clinical Trials

In clinical trials PP796 showed no evidence of protection against histamine-induced bronchospasm, no consistent effect upon blood pressure of either normotensive or hypertensive subjects, no beneficial effect on psychiatric disorders or body weight in obesity and no effect on thyroid, or adreno-cortical function.

The side-effects of PP796 dosing were nausea, vomiting and dizziness at 1mg unit doses and above. Angina pectoris appeared on chronic dosing of 2mg to two subjects.

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COPY TO: MR A W WAITT FERNHURST

ALSO COPIED TO: DR J T BRAUNHOLTZ AND DR A CALDERBANK JEALOTTS HILL

REFERENCE YOUR TELEPHONE CALL WEDNESDAY LAST PP796 DOCUMENTATION. AUTHORISATION BEING OBTAINED FROM PHARMACEUTICALS DIVISION FOR FORMAL RELEASE OF DATA TO YOURSELVES. SUGGEST THAT SOME OF DOCUMENTATION MAY NOT BE RELEVANT TO PROPOSED USAGE AND THAT IN VIEW OF TIME CONSTRAINT WE REVIEW INFORMATION DURING YOUR FORTHCOMING VISIT .

FOULKES

PLANT PROTECTION DIVISION

BRACKNELL

cc: R.D. CAVALLI.
L.R. STELZER ✓