CONFIDENTIAL

IMPERIAL CHEMICAL INDUSTRIES LIMITED
PLANT PROTECTION DIVSION
Fernhurst, Haslemere, Surrey
England

RIC4204

SUMMARY DATA SHEET No.2

'GRAMOXONE': A FORMULATION CONTAINING AN EMETIC

This Data Sheet provides information on 'Gramoxone' containing the emetic PP796. Some data on PP796 itself are included to add to that provided in the Summary Data Sheet on PP796 dated 22 July 1976, which remains valid except for Section 1, which should read:

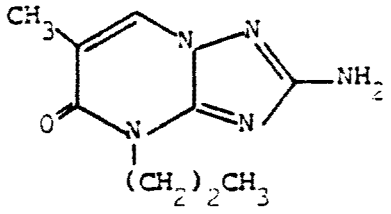
1. IDENTITY OF PP796

1.1 Chemical Name And Formula

1.1.1 Systematic name: 2-amino-4,5-dihydro-6-methyl-4-propyl-s-triazolo (1,5-a) pyrimidin-5-one. This conforms to IUPAC nonenclature.

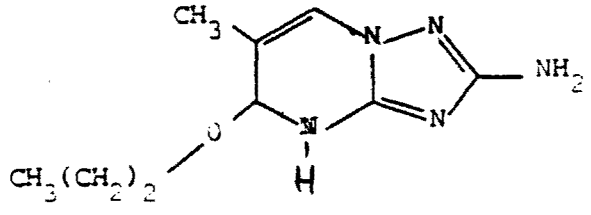
1.1.2 Empirical formula: $C_9H_{13}N_5O$

1.1.3 Structural formula:



1.1.4 Molecular weight: 207.2

1.1.5 Technical material: Technical PP796 has a purity greater than 90%. The main impurity is the 5-oxypropyl derivative, coded ICI 69, 611:-



## 2. PHYSICAL PROPERTIES

'Gramoxone' containing PP796 has been stored in representative sales containers (rigid PVC) for 3 months at 50°C and for 6 months at -5°, 0°, 25° and 37°C. There has been no evidence of physical change or loss of chemical activity.

The product has a density of 1.095 ± 0.02 g/ml.

It is non-volatile and non-flammable.

## 3. METHODS OF ANALYSIS

### 3.1. Formulation Analysis

The current method for the determination of paraquat in aqueous solutions is unaffected by the addition of PP796. PP796 is determined by the method described in July.

Reference 1

### 3.2 Residue Analysis

The determination of paraquat residues in crops is unaffected by the addition of PP796.

PP796 residues can be determined quantitatively in ryegrass and potatoes by means of gas liquid chromatography. Extracts are obtained from crop samples by maceration with cold methanol. The extracts are cleaned up by solvent partition and/or column chromatography using silica gel. Determination of PP796 is by gas-liquid chromatography, using a nitrogen selective detector. The lower limit of detection of PP796 by this method is 0.02 ppm.

Reference 2

## 4. APPLICATION

PP796 is not a pesticide and has been shown to be herbicidally inert. Its addition to 'Gramoxone' has no effect on the weedkilling properties of the product and clearance is sought for all uses on the currently cleared and approved 'Gramoxone' label.

Reference 3

PP796 will be added to'Gramoxone' at the rate of 0.05% (5mg per 10ml product). The formulation, coded JF6044, will thus consist of:

| | % w/v |
|---|---|
| Paraquat dichloride | 'x' |
| Surfactants | 5.2 |
| Pyridine Base stench | 1.0 |
| PP796 | 0.05 |
| Anti-foam | 0.01 |
| Water | to 100.00 |

Where 'x' gives 200 ± 10g paraquat per litre.

The pH is 7.0 ± 1.0. The appearance and properties of the product are not affected by the inclusion of PP796.

The method of application, mode of herbicidal action and phytotoxicity are as stenched 'Gramoxone.'

## 5. RESIDUE DATA

### 5.1. Residues in Named Crops

Potatoes have been sprayed overall with 6 litres of a formulation of 'Gramoxone' containing 500 mg PP796 per litre for weed control. The crop was 25-90% emerged at the time of spraying. Analysis of tubers harvested 6-14 weeks after spraying yielded no detectable residues of PP796.

Ryegrass treated at 3.0 and 6.0 l/ha with a similar formulation of 'Gramoxone' plus PP796 at 500 mg/litre contained PP796 residues of 0.04-0.11 ppm and 0.09-0.26 ppm respectively on the day of treatment. These levels had subsided to 0.02-0.03 and 0.03-0.05 ppm 7-8 days after application. A further trial, in which 'Gramoxone' containing 2,000 mg PP796 per litre was applied at 6.0 l/ha, yielded no detectable residues of PP796 5-6 weeks after application. These levels, where detectable, are considered to be without toxicological significance.

Reference 2

### 5.2. Taint

The taint potential of 'Gramoxone' formulations containing stench and stench plus PP796 have been compared in a trial at the Campden Food Preservation Research Association. Potatoes, variety Maris Peer, were sprayed on 14th May, at emergence, with 11.2 litres of one or other of the two formulations per hectare. Tubers were lifted on 21st July and subjected to the Association's standard taint tests. Neither fresh cooked nor canned samples showed any statistically significant difference in taste.

Reference 4

### 5.3 Persistence

a) Soil: Radio labelled $^{14}$C-PP796 has been applied to soils under both aerobic and anaerobic conditions and in the presence and absence of 'Gramoxone' (containing 1% pyridine base). Less than 2.5% of applied radioactivity was evolved as volatile $^{14}$C-labelled products irrespective of soil type and the presence of 'Gramoxone'. Amounts of radioactivity extracted decreased with time, indicating a degree of binding.

Reference 5

b) Plant surfaces: $^{14}$C-PP796 applied at approximately 75 ppm to cotton leaves in the greenhouse degraded slowly so that after 28 days only 25-30% of the applied radioactivity (40% of the radioactivity recovered) was present as PP796.
Up to 35% of the applied radioactivity was lost from the leaves. Of the remainder, 15-20% could not be extracted and approximately 20% was present as polar products.

Reference 6

c) Water: The stability of $^{14}$C-labelled PP796 in water has been assessed using concentrations of 5 ppm with and without 'Gramoxone'. Unlabelled PP796 was tested at 500 ppm in a 4% acetone/water solution. These aqueous solutions were rapidly degraded in bright sunlight, with a half-life of approximately 4 days. The rate was unchanged by the use of different sensitisers (i.e. 'Gramoxone' acetone) although the pattern of degradation products changed. One or two major and numerous minor products of photodegradation resulted.

PP796 has been applied at 5 and 50 ppm, both with and without stenched 'Gramoxone',to river waters high in microbial content. Population changes within the limits of natural fluctuation occurred during incubation but PP796 had no effect on total microbial levels.

The hydrolysis of $^{14}$C-PP796 in sterile, deionised glass-distilled water at pH levels of 5,7 and 9 kept in the dark at 25°C has been investigated. Concentrations of 5 and 50 ppm showed no significant degradation after 26 days, when approximately 90% of the applied radioactivity was recovered, approximately 95% of which was as PP796.

Reference 7

These results show that PP796 is extensively degraded by sunlight on aqueous solutions but is poorly degraded by hydrolysis in water within pH limits normally encountered naturally, in soil and on plant surfaces. PP796 had no effect on microbial populations in two representative river waters.

## 6. EXPERIMENTAL DATA ON TOXICITY

### 61.1 Acute Toxicity to Vertebrates

The 48-hr LC50 to rainbow trout is greater than 47 ppm.

Acute oral studies in the vomiting species dog and monkey have demonstrated that PP796 added to paraquat concentrations several times in excess of the LD50 to these species induced vomiting. This resulted in survival provided that it occurred within an hour of dosing. The concentration of paraquat in the plasma of animals given paraquat plus PP796 was markedly lower than that

of animals given paraquat alone. The toxicity to monkeys of paraquat formulated in the presence of an emetic does of PP796 was estimated to be lowered by a factor of approximately five.

Reference 8

Studies with a formulation identical to JF6044 but designed for export markets and containing 10% instead of 5% surfactants (JF6043) have shown the acute dermal LD50 to female rats to be 0.373 ml. formulation per kg (equivalent to 75 mg paraquat ion/kg).

The addition of PP796 to 'Gramoxone' has not altered in any way the product's skin and eye irritant properties. PP796 is not mutagenic, as shown by the Salmonella Mutation (Ame's) Test.

6.2 Effects on Man

It has been demonstrated in man, supported by data from experimental animals, that the amount of PP796 required to induce vomiting in the majority of humans ingesting it is 5 mg (0.08 mg/kg in a 60kg man). The minimum dose of 'Gramoxone' known to cause death is 10ml. JF6044 has thus been formulated to contain 5mg PP796 in 10ml product.

Reference 9

During large scale field trials in stubble carried out from August onwards, observations were made on the men engaged in spraying. No adverse effects were noted resulting from use of PP796.

As 'Gramoxone' is used widely through knapsack sprayers the chance that PP796 may produce adverse side effects, such as nausea and vomiting, under normal working conditions has also been examined. It was concluded that the level of PP796 in the atmosphere around an operators face would never reach a significant level, even if used at a concentration of 2% four times the normal rate.

Reference 10

7. MEDICAL DATA

Apart from the induction of vomiting, the symptoms and treatment of cases of oral ingestion of 'Gramoxone' with PP796 will be as for paraquat itself and are well documented. Based on human and experimental animal data it is optimistically predicted that the addition of PP796 to 'Gramoxone' will not only reduce the toxicity of the new formulation but that it will increase the likelihood of successful treatment of cases of oral ingestion.

Symptoms and treatment following skin and eye irritation remain unchanged.

8. FIELD OBSERVATIONS

No cases of harm to animals or wildlife have been reported following the spraying of some 1,000 ha during evaluation trials.

9. PERMITTED USE IN OTHER COUNTRIES

None. Applications will be made throughout West Europe and, ultimately, the world as experience is gained and supplies become available.

RDW/SC/30.11.76

## REFERENCES


1) Determination Of PP796 In 'Gramoxone' Formulations. ICI Plant Protection Division Unpublished Analytical Method, Herb 103.

2) PP796–Preliminary Method And Residue Data For 1976 UK Field Trials On Ryegrass And Potatoes. ICI Plant Protection Division Unpublished Report, AR 2704 B

3) 'Gramoxone' UK Labels (1092/Gg,1093/Fm) and Leaflet (2465/Fm).

4) Taint Tests On Samples Of 'Gramoxone' Containing Stench And Stench Plus PP796. The Campden Food Preservation Research Association, September 1976.

5) PP796 - Degradation In Soil Under Laboratory Conditions. Unpublished ICI Plant Protection Division Report, TMJ 1419B, November 1976

PP796 - An Investigation Of Its Fate On Cotton Plants In The Greenhouse. Unpublished ICI Plant Protection Division Report, TMJ 1418B, October 1976.

7) PP796: Fate in Water. Unpublished ICI Plant Protection Division Report TMJ 1417B October 1976

8) The Effect Of Administration Of An Emetic (PP796) On Paraquat Toxicity In Dog and Monkey. ICI Central Toxicology Laboratory Report, CTL/R/391, November 1976.

9) The Concentration Of PP796 Required To Produce Emesis In Experimental Animals And An Estimation Of The Emetic Dose In Man. ICI Central Toxicology Laboratory Report, CTL/R/390, October 1976.

10) Paraquat Emetic Formulation. An Estimate Of The Likely Spray Concentrations of PP796 Under Normal Working Conditions. ICI Plant Protection Division Unpublished Report, MED/76/3C, November 1976

Does not need SDS

# PP 796 - SUMMARY DATA SHEET, JULY, 1971.

The following check list correlates the data presented to the UK Authorities in July in Summary Data Sheet - PP 796 (RDW/PTV 22/7/71) with the original Pharmaceutical Division's data.

References in column 1 are to the sequential numbering of the PPD Summary Data Sheet.

References in column 2 - the source of the data - are as follows:

'Vol 1' = Submission of Evidence To The Committee On Safety Of Drugs Prior To The Introduction Into Humans Of ICI 63,197; Vol 1, Chemistry and Pharmacy, July, 1970

'Vol 2' = Ibid; Vol II, Pharmacology and Biochemistry.

'Vol 3' = Ibid; Vol III, Toxicity and Proposed Clinical Trials

'Vol 4' = Ibid; Vol. IV, Toxicity Figures.

'Bayliss' = A Summary of Clinical Results of the Phosphodiesterase Inhibitor ICI 63,197 in a Variety of Disease States

'Cream' = Application to the Licencing Authority for a Clinical Trial Certificate in Respect of ICI 63,197, Cream 0·3%, Ointment 3·0%. (undated)

'Cert. of Right' = Application to the Licensing Authority for the Issue of a Variation to the Clinical Trial Certificates of Right in Respect of ICI 63,197 June, 1973.

'Animals' = Application to the Licensing Authority for the Issue of an Animal Test Certificate in Respect of ICI 63,197; May, 1973.

| in Data Sheet | Source in Pharms Data | Ref in Data Sheet | Source in Pharms Data |
|---|---|---|---|
| 1·1 – 1·1·4 | Vol 1, p 2. | | |
| 2·1 | Vol 1, pp 2, 13. | | |
| 3·1·1 | ICI Brixham Lab; 'phone recall | | |
| 3·1·2 (table, paras 2-5) | Vol 3, pp 5 - 8 | | |
| 3·1·2 (para 1) | Vol 3, p 9. | | |
| 6·1·3 | Creams, pp 20, 21 | | |
| 6·1·4 (para 2) | Vol 2, pp 27 - 29, p 23. | | |
| (para 3) | Bayliss; p 2. | | |
| (para 3, p 4) | Davies & Hepworth, 1969; CPR095/14 | | |
| 6·— (para 1) | Vol 3, p 10. | | |
| (" 2) | Vol 3, p 11. | | |
| (" 3-6) | Vol 3 pp 12 - 16. | | |
| (" 7-10) | Vol 3, pp 17 - 22 | | |
| (" 11-13) | Vol 3, pp 24 - 28. | | |
| 6·3 | Vol 2, pp 65 - 69. | | |
| 6·4 (para 2) | Bayliss, p 2. | | |
| (" 3) | Bayliss, p 2. | | |

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IMPERIAL CHEMICAL INDUSTRIES

PLANT PROTECTION DIVISION
Fernhurst Haslemere Surrey
England

# SUMMARY DATA SHEET

## PP796

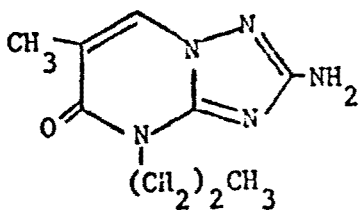
## 1. IDENTITY

### 1.1 CHEMICAL NAME AND FORMULA

1.1.1 Systematic name : 2-amino-4,5-dihydro-6-methyl-4-propyl-s-triazolo (1,5-a) pyrimidin-5-one. This conforms to IUPAC nomenclature.

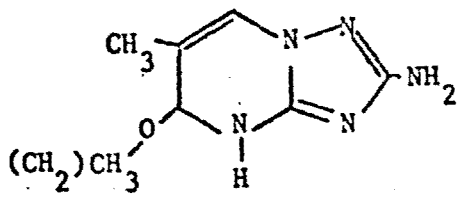
1.1.2 Empirical formula : $C_9 H_{13} N_5 O_1$

1.1.3 Structural formula :



1.1.4 Molecular weight : 207.2

1.1.5 Technical material : Technical PP796 is greater than 90% pure. The main impurity is the 5-oxypropyl derivative :



This compound is coded ICI 69,631

### 1.2 OTHER NAMES

PP796 was previously known as R50,796 and, before that, as ICI 63,197.

## 2. PHYSICAL AND CHEMICAL PROPERTIES

### 2.1 PHYSICAL PROPERTIES

Vol 1 p2, p13.

PP 796 is a white to cream crystalline powder, melting at 163-165°C and with negligible vapour pressure.

It is without smell.

PP 796 has a solubility of 2 g/litre in water, 83 g/litre in chloroform and 6 g/litre in 95% ethanol.

### 2.2 STABILITY

PP 796 has proved physically and chemically stable at room temperature (27°C) for seven years.

### 2.3 COMPATIBILITY

PP796 is compatible with and stable in aqueous solutions of paraquat, eg. 'Gramoxone'.

## 3. METHODS OF ANALYSIS

### 3.1 FORMULATION ANALYSIS

A portion of samples is diluted and the PP796 extracted into chloroform. This extract is then evaporated to dryness. For formulations containing surfactant, the residue is washed onto a Florisil column with n-hexane and the n-hexane eluant discarded. PP796 is eluted from the Florisil column using dichloromethane which is then removed by evaporation. The residue is made up to a known volume with chloroform.

An aliquot is injected into a gas chromatograph equipped with flame ionisation detection, and the peak area for PP796 is measured by electronic integrator. The PP 796 content of the sample is determined by standard comparison.

The method has been satisfactorily applied to 'Gramoxone' in which the PP796 content is 0.05% w/v.

### 3.2 RESIDUE ANALYSIS

A method for the determination of PP796 in crop tissues, soil and water is being developed.

## 4. APPLICATION

### 4.1 TYPE OF PESTS CONTROLLED

PP 796 is not a pesticide. It is to be introduced as an adjuvant in the herbicidal liquid 'Gramoxone' for the express purpose of inducing vomiting in those people who, accidently or deliberately, ingest the weedkiller.

4.2 CROPS ON WHICH THE PRODUCT WILL BE USED

All those crops, and non-crop situations, for which 'Gramoxone' is currently cleared and recommended.

4.3 FORMULATIONS FOR INTENDED USE

It is intended to add PP796 to 'Gramoxone' at the rate of 500 mg/litre. The product will thus consist of :

| | | % w/v | |
|---|---|---|---|
| Paraquat (as dichloride) | | 'x' | |
| Surfactants | | 5.2 | Where 'x' |
| Pyridine Base stench | | 1.0 | gives 200 g |
| PP796 | | 0.05 | paraquat/litre |
| Anti-foam | | 0.01 | |
| Water | to | 100.00 | |

4.4 APPLICATION, MODE OF ACTION, PHYTOTOXICITY

These will remain unchanged and will be as standard 'Gramoxone'.

5. RESIDUE DATA

Data on residues of PP796 in crops, soil and water await the development of a suitable method of analysis. Samples are being retained for this purpose.

6. EXPERIMENTAL DATA ON TOXICITY

6.1 ACUTE TOXICITY TO VERTEBRATES

6.1.1 Vertebrates other than mammals

PP796 has been screened for fish toxicity by a rapid bioassay technique using rainbow trout. The results are :

15 ppm : No effect
20 ppm : Threshold concentration for effect
30 ppm : Toxic or highly toxic

6.1.2 Mammals

The following acute LD50 values have been established :

| Species | Route | LD50 (mg/kg) |
|---|---|---|
| Rat | Oral | 150 - 155 |
| Mouse | Oral | 300 - 310 |
| Rat (Female) | Intravenous | 50 - 60 |
| Rat (Male) | Intravenous | 60 - 75 |
| Mouse | Intravenous | > 150 |

Vol 3, p9

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

Vol 3, pp 5-8.

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.

Rats dosed orally showed rapid respiration immediately after administration of 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 150 mg/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 intravenous 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.

6.1.3 Skin Irritation

Creams, pp 20, 21

PP796 0.3% cream and PP796 3.0% ointment were applied twice daily for ten consecutive days to the intact, shaved skin of six albino rabbits. 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.

6.1.4 Emetic Effects : Pharmacology

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

Vol 2, pp 23, 27-37

In tests with perfused isolated guinea pig lung, PP796 at a concentration of 5 µg/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.

Bayliss, p 2.

On this pharmacological basis the compound was investigated (as ICI 63,197) for the control of asthma in man. The human emetic response (see section 6.4) prevented further therapeutic development. The maxium tolerated non-emetic dose of PP796 in monkeys and marmosets appears to be in the range of 0.1 to 0.5 mg/kg.

## 6.2 CUMULATIVE TOXICITY

Vol 3, p 10

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

Vol 3, p 11

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

Vol 3, pp 12-16

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

Vol 3, pp 17-22

Three groups of dogs were fed 0.15, 0.5 and 1.5 mg PP796/kg 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 possible 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.

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

Vol 3, pp24-33

Both rats and rabbits dosed at 1.25 mg/kg showed signs of maternal toxicity ie. lack of appetite, poor maternal weight gain and (in rabbits) two spontaneous abortions. In rabbits, 0.75 mg/kg and 1.25 mg/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.

6.3 METABOLISM

Vol 2, pp65-69

$C^{14}$-labelled PP796 has been dosed orally 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 0.08 mg/kg; the vomit contained 42% of the dose, of which at least 93% appeared to be unchanged PP796. Monkey, rat and guinea pig produce one major metabolite common to all three species. This compound, coded ICI 68,916, is the 6-hydroxymethyl derivative of PP796. It constituted 33-38% of the total $^{14}C$ administered to the rhesus monkey, guinea pig and dog, and 15% in the rat.

6.4 EFFECTS ON MAN

PP796, as ICI 63,197, was granted a Clinical Trials Certificate (No CSD/29/77) on 23 October 1970. This was converted to Clinical Trials Certificate of Right (No. 0029/0077) on 5 August 1974.

Bayliss, p2

In clinical trials PP796 showed no consistent effect upon blood pressure of either normotensive or hypertensive subjects, no beneficial effect on body weight in obesity and no effect on thyroid, or adreno-cortical function.

Bayliss, p2.

The effects of dosing with PP796 were nausea, vomiting and dizziness at 1 mg unit doses and above. Angina pectoris appeared in two subjects following chronic dosing of 2 mg and above after four and six weeks respectively. The effects ceased on cessation of dosing. Capillary fragility with a positive Hess's Test was seen in one subject. The half-life of PP796 in man was between 1½ and 3½ hours.

7. REFERENCES

The above summary was prepared from full documentary evidence submitted by ICI Pharmaceuticals Division to Committee for the Safety of Drugs in support of a request for a Clinical Trial Certificate, subsequently granted (see section 6.4).