COMPANY SECRET

ICI PLANT PROTECTION DIVISION

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England

AN EMETIC FORMULATION OF GRAMOXONE

November 1976

AN EMETIC FORMULATION OF 'GRAMOXONE'

Efforts to reduce the risk of death from accidental or suicidal ingestion of paraquat-containing formulations have been in progress for several years. Although the addition of an emetic agent to Gramoxone has been considered in the past as a means of safening the product it had not been pursued because it was believed that no suitable emetic agents were available. The situation has changed dramatically this year with the discovery of PP796 which seems to have all the properties needed in an emetic agent to be added to paraquat formulations.

These properties are:

i That it will produce rapid and effective vomiting in man at low concentrations and with no adverse side effects. It is believed that this will greatly reduce the risk of death following ingestion of paraquat.

ii That it is stable and will not affect the physical or chemical stability of paraquat formulations.

iii That it will not adversely affect the herbicidal action of paraquat.

iv That it will not give rise to any adverse toxicological or environmental effects.

v That it will not result in too great an increase in the cost of Gramoxone.

PP796 was developed by Pharmaceuticals Division between 1968 and 1972 as a potential drug for the relief of asthma. Toxicological studies in mammals were completed to the satisfaction of the UK Committee for the Safety of Medicines, which granted a Clinical Trials Certificate. On the basis of this Certificate, trials on humans were carried out in the UK. It became clear from these trials and from data generated in monkeys and dogs that PP796 was an effective and reliable emetic agent of considerable potency.

The rapidity of action and acceptable toxicological characteristics of PP796 give it an advantage over other known emetics and it was chosen, in January 1976, as a likely candidate for addition to Gramoxone. Since then, a programme of work has fully confirmed the preliminary hopes, and is satisfying all the criteria necessary for the acceptance of PP796 as an additive to Gramoxone on a commercial scale. Work is continuing to provide information which it is believed will meet the demands of registration authorities. A summary of the important results obtained to date and of work in progress and projected are set out below.

1 Level of Addition

It is clearly crucial that PP796 should be added to Gramoxone at the right concentration. We are fortunate that results of exposing people to the compound are available from the clinical trials which

enables this level to be set. The concentration that has been selected is 0.05 w.v. ie 5 mg in 10ml of Gramoxone. This is expected to produce vomiting within 1 hour in the majority of those ingesting such a quantity, which is the approximate minimum lethal dose of Gramoxone in man. In fact most paraquat poisoning cases result from the swallowing of 20 ml or more and many suicide cases drink 50 ml or more.

2 Effectiveness in the presence of paraquat

Animal experiments have demonstrated the effectiveness of PP796 in the presence of paraquat. Dogs were dosed with paraquat at a level that killed three out of four animals within four days. All animals in a second group, given the same dose of paraquat plus PP796, vomited within 1 hour and paraquat blood levels were reduced. There were no deaths. Similar results were obtained with monkeys.

Further work has substantiated these findings. The toxicity to dogs and monkeys of paraquat in the presence of an emetic dose of PP796 has now been estimated to be lowered by a factor of about 5.

3 Toxicology of PP796

Extensive toxicological work was done by Pharmaceuticals Division including acute oral and intravenous toxicity in rats, mice and rabbits, 90 day tests in rats and dogs, a carcinogenic study in mice, teratogenic studies in rats and rabbits and dermal studies in guinea pigs and in man.

Further observations have since been made, including toxicity to fish, and acute oral, dermal, irritation and inhalation studies with the pyridine base stenched emetic formulation are in progress. PP796 is rapidly absorbed, metabolised and excreted in rats, dogs, monkeys and man.

4 Formulation

Paraquat concentrate, Gramoxone (stenched and unstenched) and Gramoxone S can be formulated with PP796 and storage tests show that there have been no physical or chemical problems with these products. PP796 can be added to appropriate formulations in pyridine bases, valeric acid (for stenched products) or an appropriate inert carrier (for unstenched product or concentrate). Systems can therefore be devised for the addition of PP796 to any paraquat product. Stability work and animal studies with paraquat mixtures with residuals, and formulation work with Weedol and Pathclear to enable emetic Weedol and Pathclear to be made are in progress or are to be started shortly.

5 Herbicidal Activity

PP796 has been shown, in glass house tests, to have no herbicidal properties.

It is virtually inconceivable that the addition to Gramoxone of PP796 at the low rate of 0.05% would have any adverse affect on the herbicidal activity of the product. This has been confirmed in a series of field tests, in which rates of addition of PP796 of up to 0.2% were examined.

6 Possible hazards to operators

PP796 is not absorbed through intact skin and has low volatility. It has a very short persistence in man. These facts, coupled with the extremely low level of PP796 in spray-strength material virtually eliminates any risk of operator hazard. Observations are now being made in the field on farm workers in the UK spraying pyridine base stenched or unstenched emetic product as part of the large-scale development. The results obtained so far have not shown any adverse effects from the emetic.

Consideration has been given to carrying out trial work overseas to ensure that no side-effects occur when the new formulation is applied from a knapsack sprayer under tropical conditions for several days continuously. Dr Howard, the Division Medical Officer, has concluded after considering all the available data, and taking into account the negative results from the UK trials, that such work will not be necessary.

7 Possible environmental and food residue hazards

When Gramoxone containing PP796 is used in agriculture only about 2g of the compound will be applied per hectare. This low rate of application provides a fair degree of assurance that its residues will not be detectable in food crops and that no environmental hazards will ensue. Work is in progress to confirm this.

A residue method sensitive to 0.01 ppm has been developed and has been used to demonstrate absence of residues of PP796 in potato tubers harvested after haulm desiccation with the emetic formulation, and to show that PP796 is lost from the surface of leaves.

Work on the environmental fate of PP796 is also in progress.

Taint tests with potatoes harvested after spraying with the new formulation were negative.

Patents

A UK patent application, disclosing emetic herbicidal compositions comprising a bipyridylium herbicide and PP796 or a close analogue, was filed on 15 April 1976. This case will be completed in the UK and filed in most countries overseas early in 1977, claiming priority under the International Convention. Foreign filings have already been made in the USA (to serve as a basis for claiming priority in some South American countries not members of the International Convention), Taiwan, South Korea and Columbia.

These patents, when granted, should prevent manufacture, import, sale or use of the patented formulations by competitors.

PP796 is protected as a new compound per se by the Pharmaceuticals Division original filing on the compound (UK patent priority 13 September 1968) which also protects the processes of manufacturing. This patent is filed in 24 countries.

The prospects of preventing competitors selling emetic formulations of paraquat seem good, since there will be very few places where they would be free to sell the product without challenging ICI's patents.

The prospects of our competitors discovering suitable emetic agents as alternatives to PP796 must be very remote. In any case we have filed patent applications in the UK on mixtures of paraquat with known conventional emetics and mixtures of paraquat with other active emetics discovered by Pharmaceuticals Division. A case covering other pesticides mixed with PP796 has also been filed.

Production

PP796 is to be manufactured by Pharmaceuticals Division and supplies will become available in sufficient quantity by March 1977 for incorporation into paraquat formulations for selected markets. Supplies in 1978 will be sufficient for addition to all paraquat products.

The final cost of PP796 to PPD has not been worked out, but it is expected that it will add about 6p or less to the cost of a litre of Gramoxone.

As indicated above, it will be possible to add PP796 to paraquat concentrate or to finished products. The method of addition for each market must now be considered bearing in mind such factors as convenience of production, liability for customs duty etc.

General Registration Strategy

To expedite registration of the new formulations it is hoped that registration authorities can be persuaded that addition of PP796 to paraquat products is a minor formulation change. At the same time we also hope to convince them that the new formulation is a major advance in our attempts to overcome the paraquat poisoning problem, because it effectively reduces paraquat's toxicity. We believe that we shall very shortly have a package of information which should amply satisfy most authorities on both these counts. We wish to ensure wherever possible as a result of the registration of the new formulation less safe formulations of paraquat will no longer be permitted.

The approach to registration authorities will therefore need to be made with these points in mind. In general the best initial approach is likely to be an informal one to acquaint the authorities with the background to the development, stressing in particular the unique nature of the formulation and the low level of addition of PP796, from which the general inference can be drawn that there are on theoretical grounds unlikely to be any hazards arising from the use of the new formulation. Wherever possible these initial approaches should also involve a visit by a CTL toxicologist or by a PPD specialist to explain the toxicological background to the development. Submission of our full dossier of information on efficacy, toxicology and environmental studies would follow shortly afterwards.

Such a process will, it is believed, obviate the need for us to submit toxicological and environmental information on the compound and the formulations as if PP796 were a pesticide, with the additional work that would be involved. However, we cannot exclude the possibility that some authorities will require additional pieces of information not provided in our initial package.

In the UK, limited clearance has already been obtained from the registration authorities (in July 1976) to permit the use of 10,000 litres of stenched Gramoxone containing PP796 on approximately 2000 ha of stubble and for other registered uses. This material was used in autumn 1976. We shall be applying for full registration of a stenched PP796-containing formulation for introduction early in 1977: the UK authorities are treating this as a minor formulation change. Registration of the current, stenched formulation will be allowed to lapse when the new product is registered.

Introduction into selected other markets is also expected from about March 1977. Very early sales (beginning of 1977) are planned in Western Samoa, where a relatively high incidence of suicides using Gramoxone is occurring: this introduction is expected to give the earliest feedback of information as to the efficacy of the new formulation.

Publicity

So far the development of PP796 has been treated as a Company Secret and, so far as is known, no information has been passed to the outside world, with the exception of a few individuals in registration authorities, who have been given the information in strict confidence.

During the next few months, the possibilities that the information about the project will become known to the public must increase and "leaks" could occur in several ways.

In addition Poisons Centres and some members of the medical profession will be told about the new formulation prior to launch because it will modify the symptoms of paraquat poisoning and could affect the approach to treatment.

In general it is believed that no label changes will be needed for the new formulation (with the exception of a clear distinguishing mark on the label for identification purposes), although a few countries may require that PP796 is identified on the label.

Since paraquat poisoning has only attracted press coverage on a significant scale in the UK and Eire, it is proposed that general publicity about the new formulation should be limited to the UK and Eire. Release of information to the press will coincide with the launch of the new formulation in the UK and Eire (probably April-May) although it is not expected that a major publicity campaign will be launched.

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APPENDIX

PP796

Chemical name: 2-amino-6-methyl-5-oxo-4-n-propyl-4,5-dihydro-s-triazolo (1,5-a) pyrimidine.