Message

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Sent: 8/31/1999 4:23:06 PM
To: Shaunak Richa R [/O=ZENECA/OU=AGUK/CN=RECIPIENTS/CN=Richa.Shaunak]
CC: Berry Dave DJ [/O=ZENECA/OU=ALDERLEY/cn=Recipients/cn=Dave.Berry]
Subject: Paraquat - Japan

Richa

As promised, following our meeting at Yalding on Friday, the information below may be useful for yourself and Fiona Gould in relation to the Japanese pressure for a "more registrable" bipyridyl product than Preeglox.

In addition to the extensive work we did on the optimisation of Magnoxone based paraquat formulations in the period 1988-1992, we did indeed move our business goals towards other markets, assuming that a global launch of a 200g/l "safer" product may not, for a number of reasons, take place all in one launch. This involved the examination of some low strength (100g/l) Magnoxone formulations (Magnoxone L). Magnoxone M5 through M8 were all 100s and had differing emetic/Mg and kelzan levels. They were very low toxicity when the emetic was pushed up. However, we soon switched to 200g/l after a Jealott's Hill TRC meeting in 1990 and developed the Magnoxone M19 YF8004 series, as you are aware.

CTL were also asked to provide data on existing registered formulations in so-called trouble spots during this period. My group examined lower strength products intended for registration in France, Hungary, Poland etc. and based our research on the formulation components used in these territories e.g. titanium dioxide/xanthan in France. We combined this with the basic concepts developed in the Magnoxone project.

Therefore, overall we have a very good data set in many dog studies on systemic exposure/plasma profile studies for PQ/DQ mixtures and for Magnoxone L . Both were compared with a Gramoxone L (100g/l) control.

These data would cover a 45g/l PQ plus 45g/ l DQ Preeglox risk assessment, as you suggested, if we base it on active ingredient i.e. slightly higher than Preeglox. We even compared low emetic Gramoxone with high emetic at 3 dose levels, for this lower strength PQ product -demonstrating a 5X safety factor with nothing else but increasing the emetic. (This is almost identical to the same work we did with standard 200g/l Gramoxone).

We examined the French formulation showing that the gelling in (Gramoxone Plus - AV 8700169) gave a product up to 10X safer with high emetic (1.5g/l) levels. This formulation was prepared by our French SOPRA group and contained 100g/l paraquat and 50g/l diquat. I have this presentation and accompanying letters to and from RAD on this and also on old Freelance overheads - not Word docs! . I was on standby to present this to the French regulators in 1991 and also have a version in French if needed!

A similar Hungarian formulation issue compared YF7970 with 0.5,1.5 and 3g/l emetic, agian in extensive dog trials. Once more, the emetic proved its benefits with the 3g/l PP796 producing remarkable improvements in tox in this thickened system.

Overall, these auxillary projects demonstrated again the benefit of the combined effects of gelling and high emetic in the reduction in acute tox. These were classified as highly confidential at the time but it would appear that we could gain some business benefit now by use of these data in a Preeglox bridging case. Fortunately, when we patented Magnoxone, we included Preeglox and all the various PQ/DQ mixes in our description. Thus, a Preeglox formulation containing Mg and gelling/purgative agents is Zeneca's intellectual property. We thought that Japan may pressurise us one day.

A good person to speak to at Fernhurst on this is Amanda Rumming. She managed both the Magnoxone and the French/Hungarian bpyridyl projects for the product development area during this period. Geoff Willis and his RAD colleagues and also Harry Swaine will remember this work also.

Without sounding too optimistic, I would be very confident in our ability to develop a very safe (10X) product at a 100g/l ai concentration.

Let me know if we need to follow this up and I would be happy to go through these data and the various reports on this I have in my files with yourself, Fiona etc.

Regards

Jon

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