Message

From: Heylings Jon GBAP [/O=MESSAGING/OU=BE-AG/CN=RECIPIENTS/CN=JON.HEYLINGS]
Sent: 11/2/2007 11:10:53 AM
To: Elliott Barry B GBAP [/O=MESSAGING/OU=BE-AG/CN=RECIPIENTS/CN=BARRY.ELLIOTT]
CC: Sheldon Ros GBJH [/O=MESSAGING/OU=BE-AG/CN=RECIPIENTS/CN=ROS.SHELDON]; Brammer Alison GBAP [/O=MESSAGING/OU=BE-AG/CN=RECIPIENTS/CN=ALISON.BRAMMER]
Subject: RE: A7813R. Clin obs & BW 64 mgkg Week 1 .doc

Barry

I agree the last study doesn't support the water loading hypothesis (at least post-dose), but the stomach contents (volume, motility and acidity etc) before and after dosing is bound to have some effect on how any compound is distributed and absorbed. Whether this is significant enough to interfere with the bioavailability of PQ in this study we just don't know.

I have found a paper copy of the signed CTL protocol XD1236 in March 1987. This is when we ran the Gramoxone and many other formulations here. This is the study where we had mortalities with high emetic Gramoxone at 48mg/kg etc.

Section 2.5 states that food was witheld for the whole of the day of dosing and water was witheld for one hour before dosing and I hour after dosing.

This was permitted in the Project Licence in force at the time. During this era there were a number of mortalities with various fromulation types, many around the 32-64mg/kg level in a 10% PQ emulsion etc. Magnoxone went up to 256mg/kg without mortalities under this protocol.

As new Licences were developed, new HO Inspectors were concerned about the animals not having access to food and water. The feeding on the day was stipulated and the free access to water at all times was also a HO requirement if we were going to use this species for this purpose. The Inteon project used these new Licence rules so there was no reason to go back to the old rules with the MPI studies.

If you recall, the Gramoxone repeats by gavage and capsule at 8mg/kg in the 1980s gave higher exposures than the more recent Gramoxones here where we were under different HO governance and could only do these studies on a Mild severity procedure that included free access to water at all times and food later that day.

I still favour the hypothesis that the animals are receiving an effective emetic dose in these non-surfactant formulations at 64mg/kg, but we need to consider these long shots.

Regards

Jon

-----Original Message-----
From: Elliott Barry B GBAP
Sent: 30 October 2007 16:32
To: Heylings Jon GBAP
Cc: Sheldon Ros GBJH
Subject: RE: A7813R. Clin obs & BW 64 mgkg Week 1 .doc

Not current level I expect. In this last set of four, 3 drank and one did not, but all the same in outcome. I know only one, but he might have been expected to show some tox more than the other three.

-----Original Message-----
From: Heylings Jon GBAP
Sent: 30 October 2007 16:30
To: Elliott Barry B GBAP
Cc: Sheldon Ros GBJH
Subject: Re: A7813R. Clin obs & BW 64 mgkg Week 1 .doc

Barry

I wonder if the MPI obs are meticulous enough to investigate this water ingestion hypothesis? For example if the survivors at expected toxic doses were observed to be high water ingesters?

Jon

----- Original Message -----

From: Elliott Barry B GBAP
To: Heylings Jon GBAP
Cc: Sheldon Ros GBJH
Sent: Tue Oct 30 17:16:09 2007
Subject: RE: A7813R. Clin obs & BW 64 mgkg Week 1 .doc

Thanks fopr comments Jon.

I asked Alison re the water and she cannot recall withdrawal happening in the recent past (her time in the area).

Barry

-----Original Message-----
From: Heylings Jon GBAP
Sent: 30 October 2007 16:12
To: Sheldon Ros GBJH
Cc: Elliott Barry B GBAP
Subject: Re: A7813R. Clin obs & BW 64 mgkg Week 1 .doc

Ros

Thanks for the data. I am on my travels at the moment but managed to open this on my blackberry.

As you say the 240 looks to be non toxic at 64 and at this dose not that different to K and even Max itself. We therefore have 2 non Inteons safe at 64. At least it looks like the stench is not involved!. The main common feature is lack of built in wetters.

One theory is there is sufficient emetic dose for these non surfactant formulations to be safe at 64 without gel etc. A key consideration is what would happen with this non Inteon 240 at the lower doses where the delivered emetic dose may not protect and the Inteon components may be important?

It may turn out that the Inteon components prevent toxicity at the low end with non wetter forms since we cannot ignore the mortalities that have occurred with Max where a sub threshold dose of emetic may have been received in the animals that had high PQ exposures.

I guess one option for the next dose of 240 is to push it to 128 but we cannot ignore the 16 territory. The best scientific test now is the built in wetter global Gramoxone at 64 but I doubt this would be sanctioned by Regulatory.

When I am back in on Friday, I will try to ascertain what we did with access to water in the first hour following dosing when we ran these studies many years ago. If an animal takes a lot of water on board after dosing it may well affect a number of digestive/emesis features as well as diluting the irritant and its ability to damage the mucosa and gain access to the blood via diffusion.

Regards

Jon

----- Original Message -----
From: Sheldon Ros GBJH
To: Akins Jonathan USGR; Allen Sandra GBAP; Brammer Alison GBAP; Brown Doug GBJH; Elliott Barry B GBAP; Heylings Jon GBAP; Lewis Dick GBJH
Cc: Botham Phil GBJH; Bembridge John GBJH; Dieterle Roland Mario CHBS
Sent: Tue Oct 30 15:44:44 2007
Subject: A7813R. Clin obs & BW 64 mgkg Week 1 .doc

<<A7813R. Clin obs & BW 64 mgkg Week 1 .doc>>

Dear all,

A7813R- a summary to date including comparison to A7813K and Gramoxone 200 A3879R. I've included a reminder of the composition of each formulation for those not as close to each formulation number/recipe.

The 24hour AUC for A7813R is likely to increase but only slightly - the samples at 7, 12 and 24 hours are analysed by a different (more sensitive) method and the data are not yet available. Dare I suggest the 24 hr AUC data point will likely end up similar to A7813K.

I have asked MPI to confirm the dose volumes and weight check of TS.
Roland, the review meeting is 2.30-3.30pm UK time if you wish to join.
Tel 020 7365 0698

Participant code 4215740#

Ros