References


[99] Lee RJ. Liposomal delivery as a mechanism to enhance synergism between anticancer drugs. Mol Cancer Ther. 2006; 5(7): 1639-40.


Appendix A. AUCC approval letters

ANIMAL USE AND CARE COMMITTEE
Private Bag X04
Onderstepoort
0110

Tel: 012-529 8434
Fax: 012-529 8300

Ref: H010-09

31 March 2009

Prof CE Medlen
Department of Pharmacology
Faculty of Health Sciences
(prof.medlen@anu.ac.za)

Dear Prof Medlen

H010-09: The toxicity and anti-cancer activity of novel drugs developed by CNSA and BioPAD sponsored “Anti cancer drug development consortium”

The application for ethical approval, dated 13 March 2009 was approved by the Animal Use and Care Committee at its meeting held on 30 March 2009.

Best regards

Elmarie Mostert
AUCC Coordinator

Copy: Dr B. Amer
Ref: H010-09 (Amendment 1)

03 June 2010

Prof CE Medlen / Dr D Cromarty
Department of Pharmacology
Faculty of Health Sciences
( connie.medlen@up.ac.za / duncan.cromarty@up.ac.za )

Dear Prof Medlen

The title addition, “Efficacy evaluation of Riminacelles™ against MDR, HCT-15 colon adenocarcinoma xenografts in Balb/C nude mice use” to the original application H010-09 “The toxicity and anticancer activity of novel drugs developed by the CANSA and BioPAD sponsored “Anti cancer drug development consortium” was approved by the AUCC

Best regards

Elmarie Mostert
AUCC Coordinator

Copy: D Koot
### Appendix B. Review of Riminophenazine QSAR

Table 1. Increased sensitivity of various Riminophenazine derivatives using non-toxic doses of Vinblastine and Doxorubicin against two Pgp expressing cell lines. Adapted from: Medlen et al. (US Patent). [166]

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<th>H69/LX4</th>
<th>K562/MMB</th>
<th>H69/LX4</th>
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Table 2. Mean IC<sub>50</sub> value (µg/ml) for various Riminophenazines against various neoplastic and normal cell cultures

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* Pgp expressing (classical resistance)
** Intrinsic non-classical resistance
Appendix C. Pharmacokinetic and tissue distribution study schedule

Day 8 (Pharmacokinetic and tissue distribution study)

55 female mice are required for this experiment.

Groups and caging

1. PTX [10 mg/kg] Riminocelles™ to 25 mice (5 cages of 5), i.e. cage A1-A5.
2. PTX [10 mg/kg] Taxol® to 25 mice (5 cages of 5), i.e. cage B1-B5.
3. Administer saline (negative control) to 5 mice (1 cage of 5), i.e. cage C1.

Experiment schedule

Before IV dosing through the tail vein, each animal was weighed and an appropriate dose calculated. Precise timing of when the dose was given and when the animal was euthanised was documented in study monitoring sheets.

07h00 Administer [10 mg/kg] PTX-Riminocelles to A1 (6 hr group).
07h25 Administer [10 mg/kg] PTX-Taxol to B1 (6 hr group).
07h50 Administer [10 mg/kg] PTX-Riminocelles to A2 (3 hr group).
08h15 Administer [10 mg/kg] PTX-Taxol to B2 (3 hr group).
08h40 Administer [10 mg/kg] PTX-Riminocelles to A3 (30 min group).
09h10 Euthanise, collect terminal blood and organ samples from A3.
09h35 Administer [10 mg/kg] PTX-Taxol to B3 (30 min group).
10h05 Euthanise Sacrifice, collect terminal blood and organ samples from B3.
10h50 Euthanise, collect terminal blood and organ samples from A2.
11h15 Euthanise, collect terminal blood and organ samples from B2.
11h40 Administer [10 mg/kg] PTX-Riminocelles to A4 (24 hr group).
12h05 Administer [10 mg/kg] PTX-Taxol to B4 (24 hr group).
12h30 Administer negative control (saline) to C1 (24 hr group).
13h00 Euthanise, collect terminal blood and organ samples from A1.
13h25 Euthanise, collect terminal blood and organ samples from B1.
14h00 Administer [10 mg/kg] PTX-Riminocelles to A5 (1 hr group).
14h25 Administer [10 mg/kg] PTX-Taxol to B5 (1 hr group).
15h00 Euthanise, collect terminal blood and organ samples from A5.
15h25 Euthanise, collect terminal blood and organ samples from B5.
Next day

11h40  Euthanise, collect terminal blood and organ samples from A4.
12h05  Euthanise, collect terminal blood and organ samples from B4.
12h30  Euthanise, collect terminal blood and organ samples from C1

\(^a\)Heparinised blood samples are to be drawn via cardiac puncture from 5 (isoflurane anaesthetized) mice at 30 min, 1 hr, 3, 6 for drug level quantitation. At 24 h two blood samples are to be drawn for both toxicity marker profiling and drug quantitation.

\(^b\)Organs (Liver, spleen, kidney, lungs and adipose tissue) are to be collected and weighed before being analysed for drug content via LC-MS/MS.