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codex alimentarius commission

FOOD AND AGRICULTURE ORGANIZATION OF THE UNITED NATIONS

WORLD HEALTH ORGANIZATION

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Agenda Item 12 **CX/RVDF 04/15/11-Add. 1**

Original Language Only

JOINT FAO/WHO FOOD STANDARDS PROGRAMME

CODEX COMMITTEE ON RESIDUES OF VETERINARY DRUGS IN FOODS

Fifteenth Session

Washington, DC (metro area), (United States of America), 26- 29 October 2004

CONSIDERATION OF THE PRIORITY LIST OF VETERINARY DRUGS REQUIRING EVALUATION OR RE-EVALUATION

Additional comments submitted in response to CL 2004/17-RVDF, Part B: Australia

AUSTRALIA

Proposal for <u>re-evaluation</u> of residues data

1. Proposal for Inclusion Submitted by: Australia
2. Drug Name: Triclabendazole
3. Trade Names: Fasinex (FASCINEX, SOFOREN) 5% Oral, Fasinex
   Fasinex (FASCINEX, SOFOREN) 10% Oral,
   FASCINEX 3%
   Fasinex 250 Tablets
   Fasinex 900 Tablets
   Fasinex 24% Oral,
   Fasimec Oral for Cattle
   Fasimec Oral for Sheep
   Genesis Ultra Pour-On,
   and others (ENDEX, COMBINEX, PARSIFAL, SOFOREN Plus 8.75 & 19.5)
4. Chemical names: 6-Chloro-5-(2,3-dichlorophenoxy)-2-methylthiobenzimidazole
5. Names and Addresses of Basic Producers:
   a. Novartis Animal Health,
   Postfach
   CH-4002 Basel
   SWITZERLAND
   b. Ancare Australia Pty Limited
   Unit 25/105A Vanessa Street, Kingsgrove NSW Australia 2208

6. Justification for Use: To control liver fluke (*Fasciola hepatica and Fasciola gigantica*) in cattle, sheep and goats by administration orally or in cattle also by pour-on.

7. Veterinary Use Pattern: Drench cattle, goats and sheep orally with drench gun or administer appropriate volume to backline of cattle

8. Countries Where Drug is Registered:

Fasinex (FASCINEX, SOFOREN) 5% is registered in Australia, France, India, Ireland, Morocco, Nepal, The Netherlands, New Zealand, Pakistan, Peru, Philippines, Portugal, Spain, Switzerland, UK, Ukraine, Uruguay.

Fasinex (FASCINEX, SOFOREN) 10% is registered in Argentina, Australia, Brazil, Chile, China, Colombia, Ecuador, Egypt, France, Germany, Indonesia, Ireland, Japan, Kenya, Mexico, Nepal, Netherlands, New Zealand, Peru, Philippines, Portugal, Russia, South Africa, Spain, Switzerland, Thailand, UK, Ukraine, Uruguay, Vietnam, Zimbabwe.

FASINEX 250: is registered in Egypt, Ethiopia, India, Nepal, Switzerland, Turkey

FASINEX 900: is registered in Egypt, Ethiopia, India, Nepal, Switzerland, Turkey

FASINEX 24% is registered in Australia, New Zealand, South Africa

FASCINEX 3% is registered in France

ENDEX 8.75% (**COMBINEX, PARSIFAL, SOFOREN Plus**) is registered in Austria, Belgium, Bolivia, Bulgaria, Egypt, India, Ireland, Nepal, The Netherlands, New Zealand, Pakistan, Peru, Romania, South Africa, Spain, Switzerland.

ENDEX 19.5% (**COMBINEX, PARSIFAL, SOFOREN Plus**) is registered in Austria, Bangladesh, Belgium, Bolivia, Bulgaria, Egypt, India, Ireland, Nepal, The Netherlands, New Zealand, Pakistan, Peru, Romania, South Africa, Spain, Switzerland, Thailand, Uruguay, Zimbabwe.

FASIMEC Sheep Oral (tradename FASIMEC Sheep Oral Flukicide and Broad Spectrum Drench) is registered in Australia

FASIMEC Cattle Oral (tradename FASIMEC Cattle Oral Flukicide and Broad Spectrum Drench) is registered in Australia

GENESIS Ultra Pour-On (tradename GENESIS Ultra Pour-On Roundworm, Liver Fluke & External Parasiticide for Cattle) is registered in Australia and New Zealand.

9. National Maximum Residue Levels (Compared with Codex):

Maximum Residue Limits (µg/kg triclabendazole)				
	Australia	New Zealand	Codex	EMEA*
Cattle				
muscle	500	200	200	100
Liver	2000	300	300	100
Kidney	1000	300	300	100
fat	1000	100	100	-
Sheep				
muscle	500	100	100	100
Liver	2000	100	100	100
Kidney	1000	100	100	100
fat	1000	100	100	-

* EU MRLs are currently being reviewed.

10. Commodities for Which the Need for Establishing Codex MRLs is Required:

    Cattle liver, kidney, muscle and fat
    Sheep liver, kidney, muscle and fat
    Goat liver kidney muscle fat

11. List of Data Available:

    a. Residue data for new route of administration (pour-on) in cattle,

    - **Report on the Synthesis of [14C]-Triclabendazole**
    - **D Needham 2004 [14C]-Triclabendazole: Distribution, and excretion following oral administration to cattle**

      (describes excretion and distribution and attempts to describe metabolism (metabolites difficult to identify despite extensive trials as they are probably covalently bound to tissues) in a bovine killed 1 month after treatment; shows similarity of residue profile in bovine and rat; confirms accountability of analytical method for cattle tissue)

    - **T Hardwick 2004 [14C]-Triclabendazole: Absorption, distribution, excretion and metabolism in the rat**

      (describes absorption, excretion, distribution and attempts to describe metabolism (metabolites can hardly be identified despite extensive trials as they are probably covalently bound to tissues) in rats killed 10 days after treatment, shows similarity of residue profile in bovine and rat)

    - **T Hardwick 2004 [14C]-Triclabendazole: Bioavailability of total residues in bovine tissues to rats**

      (confirms that bioavailability of incurred radioactive residues in bovine tissues is 20% or lower on day 28 using bile-cannulated rats (Gallo-Torres method))

    - **D Needham 2004 [14C]-Triclabendazole: Pharmacokinetics in the rat following oral and intravenous administration**

      (confirms that bioavailability of pure triclabendazole is high (70%) and of incurred residues in bovine tissues low (10% or lower) using the comparison of AUCs after oral administration of pure active substance or incurred radioactive residues versus intravenous administration of pure active substance)

    - **S Adams 2004 Determination of Residues of Triclabendazole in Animal Tissues by HPLC. Analytical Procedure 193F.00**

      (describes the scaled down and modernised analytical method for residues)

    - **S Adams 2004 Validation Of Analytical Procedure No. 193F.00**

      (describes validation of the above method)

    - **S Adams 2004 Tissue residues of triclabendazole, measured as CGA 110754, in cattle following repeated oral dosing with Fasinex 10%**

      (describes residue depletion in cattle killed on days 14, 28, 42 & 56 using modernised method)

    - **S Adams 2004 Tissue residues of triclabendazole, measured as CGA 110754, in sheep following oral dosing with Fasinex 5%**

      (describes residue depletion in sheep killed on days 14, 28, 42 & 56 using modernised method)

    A table of contents of the previously submitted data by Novartis to JECFA is attached (**Appendix 1**). These data will be resubmitted.

12. Date Data Could be Submitted to JECFA: 1 July 2005

APPENDIX 1

List of References

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Summary assessment report on triclabendazole

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Distribution, degradation and excretion of CGA 89317 in sheep.
Project Report 10/82

4. Ferguson E (1994)
[^{14}C]-CGA 89317: Absorption, distribution and excretion following a single oral administration of Fasinex®-5% to ruminating sheep.
Report number 380/215-1011

5. Hamböck H and Strittmatter J (1981)
Distribution, degradation and excretion of CGA 89317 in the lactating goat.
Project Report 34/81

6. Downs J H, Marsh J D and Krautter G R (1991)
Depletion of total drug-related residues in tissues of beef cattle treated with [^{14}C]-triclabendazole (Pilot Study).

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[^{14}C]-CGA 89317: Absorption, distribution and excretion following a single oral administration of Fasinex®-10% to ruminating cattle.
Report number 380/214-1011

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Determination of total residues of CGA 89317 in sheep muscle, liver, kidney and fat after a single oral treatment at a rate of 10 mg.kg^{-1} or 15 mg.kg^{-1} body weight.
Residue Report RVA 4005/82

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Determination of total residues of CGA 89317 in sheep muscle, liver, kidney and fat after a single oral treatment at a rate of 10 mg.kg^{-1} body weight.
Residue Report RVA 4002/83

10. Lanter F (1989)
Determination of total residues in muscle, liver, kidney and fat after a single oral treatment with Endex 8.75% suspension at a dose rate of 17.5 mg.kg^{-1} body weight (*ie* 10 mg.kg^{-1} triclabendazole and 7.5 mg.kg^{-1} levamisole hydrochloride).
Residue Report 4001/89

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Determination of total residues of CGA 89317 in cattle muscle, liver, kidney and fat after single oral treatment at a rate of 12 mg a.i.kg^{-1} body weight.
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Determination of total residues in muscle, liver, kidney and fat after a single oral treatment with Endex 19.5% suspension at a dose rate of 19.5 mg.kg^{-1} body weight (*ie* 12 mg.kg^{-1} triclabendazole and 7.5 mg.kg^{-1} levamisole hydrochloride).
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Project Report 41/83

15. Mücke W (1981)
Distribution, degradation and excretion of CGA 89317 in the rat.
Project Report 27/81

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Kinetics of unchanged CGP 23 030 and its sulphoxide and sulphone metabolites in plasma and urine of dogs, and in urine of rats, following intravenous and oral administration of single doses of ^{14}C-labelled CGP 23 030.
Report C R B R 25

17. Wiegand H, Schütz H and Probst A (1991)
CGP 23030, triclabendazole, Fasinex. Absorption and disposition studies in female rabbits.
Report D M 12

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Kinetics of unchanged CGP 23 030 and its sulphoxide and sulphone metabolites in female rabbits following intravenous and oral administration of single doses of ^{14}C-labelled CGP 23 030.
Report C R B R 22

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Project Report 50/82

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Pharmacokinetic studies carried out with CGA 89317 and its metabolites CGA 110752 and CGA 110753 in sheep.
R & D Technical Report 82/7/916

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The bioavailability of triclabendazole and its sulphoxide metabolite in cattle.
R & D Technical Report 86/12/1099

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The kinetics of triclabendazole disposition in sheep.
J Vet Pharmacol Therap, 10: 64-72.

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Project Report 3/95

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The metabolite profiles in urine and faeces extract of ruminating cattle after administration of [U-^{14}C]Benzi-Imidazole CGA 89317.
Project Report 2/95

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Method REM 15/83

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Project Report 8/94

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Project Report 6/95

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Validation of R & D analytical method No. 186.
Report SPR 17/81

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Determination of total residues in tissues and fat of sheep and cattle.
Method REM 3/83

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Validation of method REM 3/83 (Determination of total residues in tissues and fat of sheep and cattle).
Residue Report SPR 11/83

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Triclabendazole (CGA 89 317): Validation of method REM 15/83: Determination of common moiety CGA 110 754 in muscle, liver, kidney and fat of cattle as well as in muscle and liver of sheep after administration of ^{14}C-CGA 89 317 by high performance liquid chromatography (HPLC).
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Technical Report 88/1/1178

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Pharmacokinetics of triclabendazole alone or in combination with fenbendazole in sheep.
J Vet Pharmacol Ther, 9: 442-445.

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Pharmacokinetics of Fasinex 1800 boli in cattle.
Technical Report 90/5/1291

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