SOUTH AFRICAN COMMON TECHNICAL DOCUMENT

MEDICINES CONTROL COUNCIL

APPLICATION FOR REGISTRATION OF A MEDICINE

- **South African Module 1**
- **CTD-Modules 2 - 5**

MCC Edition August 2012

South African Common Technical Document

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[2] *Typically in the eCTD this logical document should consist of a single file. The CTD defines these further heading levels and navigation should be provided within the document to these subheadings.*

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[3] *Typically in the eCTD this logical document should consist of a single file. The CTD defines these further heading levels and navigation should be provided within the document to these subheadings.*

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APPENDIX A: Examples of Tables and Figures for Written Summaries

The tables and figures in Appendix A are presented merely as examples. Applicants should provide tables and figures using a format appropriate to the product.

Study references should be included in the table or text.

Tables should include statistics, if appropriate.

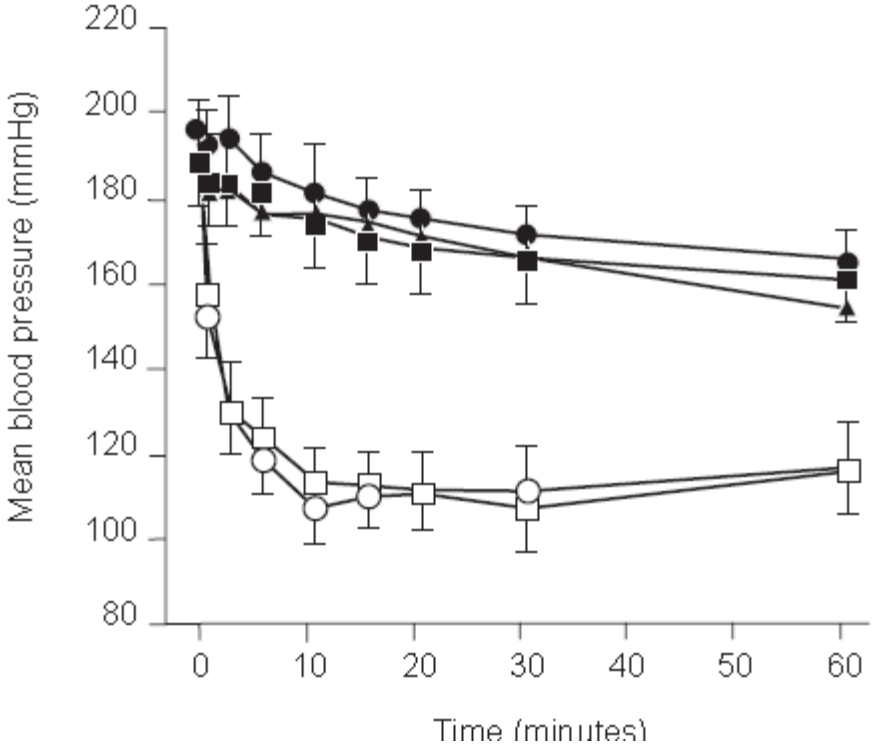
Table X

Binding of X and its Major Metabolites and Comparators to Human X_2 and X_3 Receptors

Compound	X_2 K_i1(nM)	X_2 K_i2(nM)	X_3 K_i1(nM)	X_3 K_i2(nM)
1	538	2730	691	4550
2	2699	1050	2.0	181
3	578	14.4	141	10400
4	20	100	10.7	7.9
5	2100	3.1	281	28
6	7.5	8.4	44	2.8
7	3.11	3.76	1.94	1.93

K_i1 and K_i2 represent the high and low affinity binding sites respectively (Data from Study Number).

Figure X: Blood Pressure Following Chronic Dosing With X to SHR[a]



Blood pressure following chronic dosing with X to SHRa[ref].
Hypotensive effect of saline i.v. infusion over 5 min (s) compared to X, 3 mg/kg i.v. infusion to SHR pretreated twice daily with saline, 1 mL/kg p.o., for 7 (m) or 14 (p) days or X, 25 mg/kg p.o., for 7 (l) or 14 (n) days.
Saline pretreated statistical significances: $p<0,05$, all other points after challenge $p<0,01$. Values represent mean ± s.e.m.

aSHR= spontaneous hypertensive rate (n=5 per group)

Table X

Model-independent pharmacokinetic parameters for X in mice following single oral doses at 2, 10 and 30 mg/kg [ref]

Parameter (units)	**Parameter value**					
Sex	**Males**			**Females**		
Dose (mg/kg)	2	10	30	2	10	30
C_{max} (ng/mL)	4.9	20.4	30.7	5.5	12.9	28.6
T_{max} (h)	0.8	0.4	0.3	0.4	0.5	0.3
AUC_{0-t} (ng.h/mL)	21.6	80.5	267	33.3	80	298
AUC_{0-inf} (ng.h/mL)	28.3	112	297	40.2	90	327

Pharmacokinetic parameters were determined in pooled plasma from three animals at each time

Table X: Excretion of radioactive material following single doses of [^{14}C]X to male mice [ref]

Dose (mg/kg)/ route		Percentage of administered dose		
		Urine*	Faeces	
2.8	i.v.	88.1 ± 7.4	5.5 ± 0.7	93.6 ± 6.9
8.8	p.o.	89.4 ± 4.7	6.9 ± 1.4	95.3 ± 3.4

Excretion was determined over 168 hours after dosing
Values are means ± S.D. (n= 5 for p.o. and 5 for i.v.)
* - includes radioactivity in cage wash (22.1% after p.o. and 21.7% after i.v.)
+ - includes radioactivity in the carcass

Table X: Concentrations of Radioactive Material in the Tissues of Male Rats After a Single Intravenous Dose of [^{14}C]X at 1.75 mg/kg [refs]

Tissue	Concentration (ng equiv.*/g)				
	1 h	6 h	24 h	48 h	72 h
Blood	105	96.6	2.34	2.34	3.65
Plasma	142	175	3.12	ND	ND
Adrenals	656	49.2	14.3	9.63	ND
Bone marrow	359	31.5	ND	ND	ND
Brain	116	9.37	ND	ND	ND
Eyes	124	28.9	4.69	ND	ND
Fat	490	44.0	10.2	6.25	5.47
Heart	105	26.6	ND	ND	ND
Kidneys	1280	651	21.6	13.3	9.63
Large intestine	570	2470	39.3	12.0	ND
Liver	875	380	133	87.7	64.6
Lungs	234	59.1	7.55	ND	ND

* - ng of X free base equivalent/g.
N = 5 animals/time point
ND - Not detected

Table X: Excretion of Radioactive Material Following Single Doses of [^{14}C]X to Male Rats [refs]

Dose (mg/kg)/ route		Percentage of administered dose			
		Urine	Feces	Bile	Total
1.75	i.v.	61.3 ± 9.3	30.3 ± 4.1	-	95.2 ± 5.0
1.75	p.o.	57.4 ± 3.8	37.0 ± 3.4	-	95.2 ± 1.5
2	p.o.	72.3 ± 0.8	26.9 ± 1.9	-	99.5 ± 1.1
20	p.o.	23.5 ± 6.3	0.5 ± 0.2	76.0 ± 5.9	100 ± 0.8
220	p.o.	67.1 ± 9.0	24.8 ± 5.0	-	93.3 ± 6.8

Excretion was determined over 168 h period in Wistar rats:Values are means ± S.D. (n=5); - not assayed; Total includes radioactivity in the carcass and cage washings.

Table X: Comparative Pharmacokinetic Data and Systemic Exposure to X Following Oral Administration to Mice, Rats, Dogs, and Patients [ref]

Species (formulation)	Dose (mg/kg/day)	Systemic (plasma) exposure		References
		C_{max} (ng/mL)	AUC (ng.h/mL)#	
Man (tablet)	0.48$	36.7	557	X
Mouse (solution)	8.8	68.9 (1.9)*	72.7 (0.2)*	Y
	21.9	267 (7.3)*	207 (0.5)*	
	43.8	430 (11.7)*	325 (0.7)*	
Rat (solution)	50	479 (13.0)*	1580 (2.8)*	Z
Dogs (solution)	1.5	5.58 (0.2)*	15.9 (<0.1)*	V
	5	24.8 (0.7)*	69.3 (0.1)*	
	15	184 (5.0)*	511 (0.9)*	

Data presented are for male and female animals and are after daily repeated oral administration (at the end of the 60-day mouse study, 14 day rat study, and 1 year dog study). Data for man are extrapolated from dose normalised data obtained in male and female patients following t.i.d. regimen.

- AUC0-6 in the mouse, AUC0-t in the rat and in the dog and dose normalised AUC0-τ x 24 in man.

$ - calculated from the total daily dose assuming a bodyweight of 50 kg for man.

* - Numbers in parentheses represent ratios of exposure in animals to those in patients.

Table X: Incidence of Proliferative Interstitial (Leydig) Cell Lesions in Rats [ref]

	Dose Groups			
Lesion	**Control**	**3 mg/kg**	**30 mg/kg**	**100 mg/kg**
Hyperplasia (only)	x/50 (%)	x/50 (%)	x/50 (%)	x/50 (%)
Adenoma (only)	x/50 (%)	x/50 (%)	x/50 (%)	x/50 (%)
Adenoma + Hyperplasia	x/50 (%)	x/50 (%)	x/50(%)	x/50 (%)
Total*	x/50 (%)	x/50 (%)	x/50 (%)	x/50 (%)

* Adenoma and/or Hyperplasia

APPENDIX B: The Non-clinical Tabulated Summaries – Templates

Refer to the European Commission, NTA, Vol. 2B-CTD, Module 2, edition 2003 for examples of templates

2.6.3 Pharmacology

2.6.3.1 Pharmacology: Overview

2.6.3.2 Primary Pharmacodynamics*

2.6.3.3 Secondary Pharmacodynamics*

2.6.3.4 Safety Pharmacology

2.6.3.5 Pharmacodynamic Medicine Interactions*

2.6.5 Pharmacokinetics

2.6.5.1 Pharmacokinetics: Overview

2.6.5.2 Analytical Methods and Validation Reports*

2.6.5.3 Pharmacokinetics: Absorption After a Single Dose

2.6.5.4 Pharmacokinetics: Absorption after Repeated Doses

2.6.5.5 Pharmacokinetics: Organ Distribution

2.6.5.6 Pharmacokinetics: Plasma Protein Binding

2.6.5.7 Pharmacokinetics: Study in Pregnant or Nursing Animals

2.6.5.8 Pharmacokinetics: Other Distribution Study

2.6.5.9 Pharmacokinetics: Metabolism *In Vivo*

2.6.5.10 Pharmacokinetics: Metabolism *In Vitro*

2.6.5.11 Pharmacokinetics: Possible Metabolic Pathways

2.6.5.12 Pharmacokinetics: Induction/Inhibition of Medicine-Metabolizing Enzymes

2.6.5.13 Pharmacokinetics: Excretion

2.6.5.14 Pharmacokinetics: Excretion into Bile

2.6.5.15 Pharmacokinetics: Medicine-Medicine Interactions

2.6.5.16 Pharmacokinetics: Other

2.6.7 Toxicology

2.6.7.1 Toxicology: Overview

2.6.7.2 Toxicokinetics: Overview of Toxicokinetics Studies

2.6.7.3 Toxicokinetics: Overview of Toxicokinetics Data

2.6.7.4 Toxicology: Active Pharmaceutical Ingredient

2.6.7.5 Single-Dose Toxicity

2.6.7.6 Repeat-Dose Toxicity: Non-pivotal Studies

2.6.7.7 Repeat-Dose Toxicity: Pivotal Studies

2.6.7.8 Genotoxicity: *In Vitro*

2.6.7.9 Genotoxicity: *In Vivo*

2.6.7.10 Carcinogenicity

2.6.7.11 Reproductive and Developmental Toxicity: Non-pivotal Studies

2.6.7.12 Reproductive and Developmental Toxicity: Fertility and Early Embryonic Development to Implantation (Pivotal)

2.6.7.13 Reproductive and Developmental Toxicity: Effects on Embryofoetal Development (Pivotal)

2.6.7.14 Reproductive and Developmental Toxicity: Effects on Pre- and Postnatal Development, Including Maternal Function (Pivotal)

2.6.7.15 Studies in Juvenile Animals [a]

2.6.7.16 Local Tolerance

2.6.7.17 Other Toxicity Studies

* : Tabulated Summary is optional. It is preferable to include text tables and figures with the Nonclinical Written Summary.

[a] : When a juvenile animal study has been conducted, it should be tabulated using the template appropriate for the type of study and located in Section 2.6.7.15.

UPDATE HISTORY

Date	Reason for update	Version & publication
November 2009	First publication released for pilot implementation	v2 Nov 2009
June 2010	Released for implementation	v2 June 2010
March 2011	Amended after first pilot submissions and workshop with industry	v3 March 2011
	Amended module headings 1.2.2.6, 1.2.2.7, 1.2.2.8 1.3.1, 1.3.2 – added 1.3.1.1, 1.3.1.2 1.5.2.1 Added 1.5.5 1.7.1, 1.7.2, 1.7.3, 1.7.4 – added new 1.7.1, & 1.7.2; 1.7.5, 1.7.6, 1.7.7, 1.7.8, 1.7.9, 1.7.10 – removed 1.7.10.1, 1.7.10.2 Removed 1.7.11 Renumbered 1.7.12, 1.7.13 Added new 1.7.13 Removed 1.10.5, 1.10.6 Removed 1.11.3.1 to 7	
	3.2.R.1, 3.2.R.1.1 Removed 3.2.R.1.2 and renumbered 3.2.R.1.1.8, 3.2.R.1.1.11 3.2.R.1.2 – 3.2.R.1.1.2, 3.2 R.1.1.5 Removed 3.2.R.1.2.16.1 – 4 Renumbered 3.2.R.4, renumbered; Removed 3.2.R.1.4.1.1 – 5 3.2.R.2 Moved 3.2.R.6 to 3.2.R.3 and renumbered 3.2.R.4, 3.2.R.4.2, 4.3.R.4.4, added 3.2.R.4.3 3.2.R.6, 3.2.R.7	
1 June 2011	Date for implementation	
August 2011	Amendment to 1.7.7/8/9 for immediate implementation	v4 August 2011
August 2012	Amendment to 1.5.5 for immediate implementation	v5 August 2012