MEDICINES CONTROL COUNCIL

DEPARTMENT OF HEALTH
Republic of South Africa

MEDICINES CONTROL COUNCIL

CLINICAL

This guideline is intended to provide recommendations to applicants wishing to submit applications for the registration of medicines. It represents the Medicines Control Council's current thinking on the safety, quality and efficacy of medicines. It is not intended as an exclusive approach. Council reserves the right to request any additional information to establish the safety, quality and efficacy of a medicine in keeping with the knowledge current at the time of evaluation. Alternative approaches may be used but these should be scientifically and technically justified. The MCC is committed to ensure that all registered medicines will be of the required quality, safety and efficacy. It is important that applicants adhere to the administrative requirements to avoid delays in the processing and evaluation of applications.

Guidelines and application forms are available from the office of the Registrar of Medicines and the website.

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REGISTRAR OF MEDICINES
MS M.P. MATSOSO

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1 INTRODUCTION

Guidelines are constantly evolving as a result of scientific developments and harmonisation of the requirements of the major overseas regulatory authorities. The Medicines Control Council endeavours to keep abreast of such developments and keep its application requirements and evaluation policies in line with "best international practice". Please refer to the Clinical trial guideline.

Legislation to be read in conjunction with these guidelines:

- The Act
- The Regulations to the Act.
- Medicine registration application form - MRF1 PARTs 4 and 5.

2 PRE-CLINICAL STUDIES (MRF1 PART 4)

The details of results from tests shall depend on the state of scientific knowledge at the time when the application is lodged. Any interim and final results of ongoing studies should be submitted as soon as these data become available.

A new route of administration, or an increased daily dose of unknown inactive pharmaceutical ingredients, may result in the need for additional pharmaco-toxicological data.

2.1 Biological medicines

Details (published or unpublished) of the results of any trials or experiments carried out in man or in the animal target species, or carried out in other animals, that establish and confirm the safety of the medicine, with particular reference to the dosage and directions for use, should be included.

2.2 Pharmacology

For medicines other than biological medicines the Pharmacology of the medicine should be addressed.

2.2.1 Pharmacodynamics:

a) The primary effects of the medicine, with results in different animal species (ED_{50} values if possible), should be addressed.

b) Comparison of the effects of the product with that of reference products, is valuable information.

c) Where relevant, the pharmacology of significant metabolites should be investigated.

d) Other pharmacodynamic effects, especially those that might be of significance for adverse effects of the medicine, should be studied and described.

Interaction studies, where **relevant**, should be included.

2.2.2 Pharmacokinetics:

a) To assist in the interpretation of toxicological studies, it is important to compare the exposure of the animals used in the toxicity testing with that anticipated in patients given the proposed therapeutic dose regimen. data, which includes C_{max} (after a single dose and at steady state) and AUC

b) PART 4 should, therefore, include comparative pharmacokinetics data for the parent drug and major/active metabolite(s), where relevant, in human and all species used in the toxicity, carcinogenicity and reproduction studies.

c) These data should preferably be obtained from the toxicity studies.

d) Other information (for example, $t_{½}$ and clearance) may be of value where important differences have been shown between animals and man.

2.3 Toxicology:

For medicines other than biological medicines the Toxicology of the medicine should be addressed.

a) A summary, or Expert Report, should be submitted for each animal species studied, with information on the sex of the animals, number of animals, dosage, route of administration, duration of study and toxic manifestations.

b) Important points to consider that pertain to pre-clinical toxicity, are:

- Dose-response relationship
- Time-response relationship
- Species specificity
- Target organ specificity
- Reversibility/irreversibility of toxic effects.

c) Medicines that show specific toxicological effects, such as immunotoxicity, hepatotoxicity or neurotoxicity, should be investigated further, taking into account the points under b) above.

d) New medicines, which belong to classes that are known to produce a particular toxic effect, should be tested appropriately.

e) The possible mechanism(s) underlying the changes observed in toxicity studies need to be investigated and addressed.

f) Due to the local climatic conditions, the phototoxic potential of a medicine, should be considered.

g) The points to address in the reproduction studies include: fertility, embryonal toxicity, teratogenicity, peri- and post- natal effects.

3 CLINICAL STUDIES (MRF1 PART 5)

3.1 The clinical data should be presented in a manner that allows easy cross-referencing to the index, other studies and the package insert. [Applicants wishing to submit data in electronic form should discuss the requirements with the Registrar.]

3.2 Data presented in support of the safety and efficacy of the medicine should be derived from clinical trials conducted in compliance with internationally accepted GCP guidelines. The studies should be properly designed and conducted, and should be of acceptable statistical power. (Refer to the Clinical Trial guideline). Where relevant, results published in peer reviewed scientific journals, should be submitted.

3.3 Clinical trials should be conducted with the formulation as applied for. Where studies have been conducted with different formulations, comparative equivalence studies are required to enable extrapolation to the formulation intended for the market.

3.4 Normally individual patient data from clinical trials need not be included in an application dossier (except in the case of bioequivalence studies where the individual plasma/serum concentrations and derived pharmacokinetic data should be supplied). Tabulated individual patient data may be included in the application if the applicant considers it appropriate.

3.5 Studies designed to demonstrate the pharmacodynamics of a medicine should address the effect of the medicine, duration of effect, dose-response and tolerance. Additional action on e.g. the central nervous system, respiration, circulation, blood chemistry, liver and kidney function should be considered at the proposed therapeutic dose(s).

3.6 Pharmacokinetic studies should be conducted with the formulation as applied for. All relevant pharmacokinetic data shall be given, such as amount and rate of absorption after various routes of administration, plasma concentration, half-lives, drug clearance, drug metabolism, as well as the routes and rates of excretion.

The pharmacokinetic studies should be carried out with both single dose and multiple doses to steady state within the recommended dosage range. Where applicable the plasma concentration(s) producing pharmacological and/or therapeutic effects as well as adverse effects, should be presented.

Possible dose-dependent pharmacokinetic effects should be addressed.

3.7 The trial design of the relevant clinical studies should be such that the safety and efficacy of the medicine can be established in comparison to either placebo and/or a registered medicine in the UK, USA, Sweden, Canada, Australia and EU.

The description of the studies should include patient population size and diagnosis, in- and ex-clusion criteria, test and comparator / reference drug dosage regimens and duration of therapy, parameters assessed for efficacy and safety, including results of special investigations.

Detailed statistical results should be presented. It should be noted that the randomised, double blind, placebo and/or active controlled trial design remains the gold standard for establishing the efficacy and safety of medicines.

3.8 The dosage of the active comparator / reference should be in line with that approved for the specific indication.

3.9 The patient drop-outs should be addressed, including the time of and reason(s) for withdrawal/drop-out.

3.10 To enable evaluation of safety of the medicine it should be noted that the long-term safety, particularly for medicines proposed for chronic use, should be addressed.

3.11 Whilst the product is in the evaluation process Applicants should notify the MCC of:

a) any approvals, rejections or withdrawals of applications in other countries and

b) any serious adverse effects observed for the first time or at a frequency which has become a concern

c) new significant data which is contrary to the use of the medicine which becomes available. The notification should include the Applicant's further intention regarding the application.

4 SBRA

The SBRA is intended to be a very brief and concise document containing the core data, on the basis of which, the applicant intends to obtain registration for the product. It is to be presented as a summary only. Hence, e.g. no articles or reports should be incorporated into the SBRA, nor should such papers be attached to it either, as these belong with the full submission.

Applicants should ensure that the general quality of the studies, proper cross-referencing to the data, explanatory notes and the quality of photocopying and binding, are of an appropriate standard. The SBRA should be cross-referenced with the documentation submitted to the Medicine Control Council.

Adaptation to the format prescribed in below, to suit each individual product/dosage form at the discretion of the applicant where specific items are not applicable, may be necessary. Applicants are kindly requested to leave a wide left-hand margin (of at least 5 cm), for office use.

Refer to the format of an SBRA (4.1) and a hypothetical example (4.2) below.

4.1 FORMAT

SUMMARY BASIS FOR REGISTRATION APPLICATION (SBRA)

4.1.1 THIS APPLICATION INVOLVES:

a new application;
or
a resubmission;
or
a package insert amendment.

4.1.2 DATE OF THIS SBRA:

a) Submitted:
b) Discussed (office use):
c) Comment to applicant (office use):

4.1.3 PRODUCT DETAILS:

- Active pharmaceutical ingredients(s) and quantity thereof:
- Proprietary name:
- Applicant:
- Application/Registration No.:
- Pharmacological classification:
- Dosage form:

4.1.5 PROVEN (ESTABLISHED) PHARMACOLOGICAL ACTION:

(Only information concerning the clinical issues and indications claimed are relevant). (MAXIMUM 100 WORDS).

(At least two key references in support of claims, preferably published, should be provided – see 13 below).

4.1.6 EVIDENCE OF EFFICACY IN HUMANS:

Data should be summarised in tabulated format, preferably under the following headings, as applicable:

a) Key trial(s) reference number: as listed under item 13 of SBRA

b) Trial design: indicate with abbreviations/symbols, e.g.

- DNB = double-blind
- SB = single-blind
- 0 = open
- X = cross-over
- P = parallel groups
- R = randomised
- C = controlled
- PC = placebo-controlled
- MC = multicentre
- LS = Latin square

4.1.6 Evidence of efficacy in humans continued:

c) Indications/Diagnosis.

d) Number of patients treated with each drug.

e) Dosage range used.

f) Duration of treatment.

g) Reference/comparative drug(s).

h) Parameters evaluated/findings.

i) Statistical data

(Please indicate separately, the total (overall) number of patients treated with the product)

Indicate clearly which trials were done/not done with the formulation and dosage form for which registration is being applied (as reflected in Part 2B of MRF).

(Free comment, if required, MAXIMUM 200 WORDS, excluding tabulated data).

4.1.7 MAIN SAFETY ISSUES AND TOXICOLOGY:

a) Human studies:

(List side effects/adverse reactions/toxicological profile, with incidence figures and key references).

b) Pre-clinical studies:

(Animal and in vitro toxicology data) (Free comment, if required, MAXIMUM 200 WORDS, excluding tabulated data).

4.1.8 EVIDENCE OF LONG TERM SAFETY/EFFICACY:

Tabulate key long-term studies, their duration, indications, findings, tolerability, etc. with references, where applicable). (Free comment, if required; MAXIMUM 100 WORDS).

4.1.9 EVIDENCE OF BIOAVAILABILITY AND PHARMACOKINETICS:

(Methods used and number of subjects studied to be clearly specified, where applicable. Pharmacokinetic data, summarised in tabular or graphical form, are essential). (MAXIMUM 100 WORDS).

4.1.10 MULTIPLE ACTIVE PHARMACEUTICAL INGREDIENTS:

For medicines containing more than one active component, provide a summary of evidence (with key references), that each contributes materially to the efficacy of the product. (MAXIMUM 100 WORDS).

4.1.11 REGISTRATION STATUS IN OTHER COUNTRIES:

Country	Date of registration

4.1.12 PROPOSED SCHEDULING STATUS:

(Provide reasons briefly, and illustrate structural formula)

4.1.13 LIST OF KEY REFERENCES:

(MAXIMUM 25)

(Directly applicable publications in refereed scientific journals are preferred. Where suitable published scientific documentation is lacking, selected unpublished key scientific reports or in-house documents may be quoted, provided these are clearly indicated as such.

The "Vancouver Style" of setting out published references, detailed below, should be used.*

Author(s), title of article, name of journal (abbreviated according to Index Medicus), journal particulars (year, volume, page no.).

Example:

1. Smith J. Treatment of mild hypertension. *Br Med J*., 1981; 283 - 628.

*Please refer to: "Uniform requirements for manuscripts submitted to biomedical Journals". S Afr Med J 1981;60:263-268).

4.2 HYPOTHETICAL EXAMPLE OF AN SBRA

SUMMARY BASIS FOR REGISTRATION (SBRA)

1 THIS APPLICATION INVOLVES:

A new application

2 DATE OF THIS SBRA:

2.1 Submitted: 01-10-1986
2.2 Discussed:
2.3 Comment to applicant:

3 PRODUCT DETAILS:

3.1	Active ingredient(s) and quantity thereof:	Rosalone 10 mg
3.2	Proprietary name:	ROZIN
3.3	Applicant:	ROSEPHARM Laboratories
3.4	Application/Registration No:	
3.5	Pharmacological classification:	6.1 Cardiac stimulants
3.6	Dosage form:	film-coated tablets

4 NAME(S) of registration Person and/or Medical Adviser responsible for compilation of this application:

Name	Position	Qualifications	Tel. No.
Mr J Smith	Registration Manager	B.Sc (Pharm)	011-9628413
Dr P Jones	Medical Director	M.B., Ch.B.	012-488327

5 PROVEN (ESTABLISHED) PHARMACOLOGICAL ACTION:

Rosalone is a positive inotropic agent with direct vasodilator activity and is different in structure and mode of action from either digitalis glycosides, or catecholamines. Rosalone produces clinically and statistically significant improvements in haemodynamic indices of congestive heart failure without significant increases in heart rate or myocardial oxygen consumption. Haemodynamic improvements are both dose and plasma level-related. In addition to increases in contractility, rosalone improves diastolic function as evidenced by improvements in left ventricular diastolic relaxation.

(References: 1, 2 and 6)

6 EVIDENCE OF EFFICACY IN HUMANS:

Key Ref No.	Trial Design	Indications/ Diagnosis	No. of patients entered & (completed)	Dosage, dosage form (formulation)	Duration of treatment	Reference Drug and dosage	Parameters evaluated/ findings	Statistical data
	O, MCDB, R, X, PC	Congestive heart failure (CHF)	92 (80)	1 0 mg/day *(f.a.a.f)	6 weeks	Placebo	a)…… b)…… c)……	p < 0.01 for all parameters except (c)
	O, X	CHF	55 (51)	20 mg/day (capsule)	4 weeks	Digoxin (0,25 mg/d)	d)…….	Not done
	O, MC	CHF	214 (189)	10 mg/day *(f.a.a.f)	14 weeks	-	…….	…….
2	DB, R, P, PC	CHF	20 (16)	20 mg/day *(f.a.a.f)	2 weeks	Placebo	…….	…….
5	DB, R, P	CHF	76 (63)	10 mg/day *(f.a.a.f)	8 weeks	Digoxin (0,25 mg/d)	…….	…….

TOTAL NUMBER OF PATIENTS TREATED ALL CLINICAL TRIALS WITH ROSALONE: 618
TOTAL NUMBER OF PATIENTS COMPLETED THERAPY 562
See also item 8

All studies (listed under items 6 and 8), except ref. 5, were done with dosage form and formulation for which registration is being applied for; (*=formulation as applied for).

7 MAIN SAFETY ISSUES AND TOXICOLOGY:

7.1 Human studies:

Effect	Incidence	Key ref.
Ventricular arrhythmias	12,6 %	13
Supraventricular arrhythmias	3,6 %	13,3
Hypotension	3,1 %	13
Angina/Chest pain	1,4 %	5
Headaches	4,4 %	4, 12, 13
Hypokalaemia	0,7 %	15
Tremor	0,5 %	8
Thrombocytopenia	5 %	13
Alkaline phosphatase	9 %	8, 13, 15

Allergic reactions occurred in +1,4 % of patients.
Dermatological reactions (rash, pruritus, etc.) were reported in + 20 % of patients. Despite this, patient acceptance and compliance was very good.

7.2 Pre-clinical Studies

			INCIDENCE	KEY REF.
A] Acute Toxicity studies	(i)	LD50: Rabbit (i.v.) 16 mg/kg Mouse (s.c.) 140 mg/kg Dog (p.o.) 400 mg/kg		(11)
	(ii)	Dog p.o. LD50: severe emesis.		(11)
B] Subacute Toxicity Studies (4 weeks)	(i)	Marked increase in Heinz inclusion bodies at 300 mg/kg p.o (Rat)	25 %	(11)
	(ii)	Elevated reticulocyte count in males given 80 mg/kg i.p., coupled with polychromasia (Rat)	1/10	(11)
	(iii)	Plasma urea 48 % higher (80 mg/kg) (Rat) i.p.	3/10	(11)
	(iv)	Crystal-like structures detectable in some tubuli of high dosed male rats.	2/5	(11)
	(v)	Allergenic reaction 40 mg – 80 mg/kg p.o. in 3 dogs at beginning of study.	30/40	(9)
	(vi)	Evidence of functional and morphological kidney damage in monkeys given 40 and 80 mg/kg (i.v.). Serum urea and creatinine increased.	3/12	(9)
	(vii)	Evidence of functional and morphological kidney damage observed in 2/4 monkeys at 30 mg/kg. Crystalline precipitates observed.	12 % 2/4	(9)
C] Subchronic Toxicity studies	(i)	Reduced erythrocyte counts and reduced haemoglobin and haematocrit values in high-dose monkeys (18 mg/kg i.v.)	8/20	(7)
		Crystalloid substances in distal tubules of 2 high-dose monkeys	2/15	(7)
	(ii)	Crystals in urine sediment (rats)	7/10	(7)
	(iii)	Death of 3 high-dose rats (500 mg/kg).	3/10	(7)
D] Chronic Toxicity (6 months)	(i)	Crystals observed in urine sediment of 2 males and 2 females from high dose group (500 mg/kg p.o.) [Rats]	4/20	(7)
	(ii)	Histopathological examination revealed mild to moderate foreign body reaction in kidneys of 2 monkeys receiving 90 mg/kg. Kidney changes were associated with intra-tubular crystallisation, but no indication of functional impairment.	2/10	(7)
E] Oculotoxicity	(Rhesus monkeys) No oculotoxicity observed			(7)
F] Arthropathy	Articular cartilage damage (juvenile rats) Lesions in articular cartilage (dogs)		11/20 12/12	(7) (7)

Hypothetical example of an SBRA continued

G] Fertility	(i) Slight decrease in implantations (no statistically significant) at 100 mg/kg dose (rat). (ii) No untoward effect on fertility or reproductive performance (Rabbit)		(7) (7)
H] Reproduction	(i) Maternal toxicity but no teratogenicity (rabbits) (ii) No maternal toxicity (rabbit) (iii) No maternal toxicity/embryotoxicity/teratogenicity (mouse) (iv) No maternal toxicity/embryotoxicity/teratogenicity (Rat)		(7) (7) (7) (7)
I] Mutagenicity/ Oncogenicity	None observed (*in vitro*; as well as in rats)		(11)

8 EVIDENCE OF LONG TERM SAFETY/EFFICACY:

Key Ref No.	Trial Design	Indications/ Diagnosis	No. of patients entered and (completed)	Dosage, dosage form (formulation)	Duration of treatment	Reference Drug and dosage	Parameters evaluated/ findings	Statis-tical data
4	O, MCDB, R, P	CHF	112 (91)	10 mg/day (f.a.a.p)	30 weeks	Digoxin (0,25 mg/ day)	……	……
*8		CHF	214 (189)	10 mg/day (f.a.a.p)	14 weeks		……	……

(* Also included under item 6) (f.a.a.p. = formulation as applied for)
N.B.: No tolerance developed during any of the clinical studies.

9 EVIDENCE OF BIOAVAILABILITY AND PHARMACOKINETICS:
Pharmacokinetic parameters for rosalone (n=24)

Parameter	Units	Mean	S.E.M.	Range
Cmax	µg/ml	120,1		97,3-154,0
Serum-protein binding	percent (%)	50,4	4,25	27,1-59,9
AUC 0-24 hr (trapezoidal)	µg.hr/ml	231,8	2,65	178,8-285,8
$t_{\frac{1}{2}}$	hr	0,15	9,18	0,04-0,33
$t_{\frac{1}{2}}$	hr	10,06	0,02	8,68-12,35
	hr	0,75	0,86	0,42-1,17

Hypothetical example of an SBRA continued

Parameter	Units	Mean	S.E.M.	Range
T_{max}	% of dose	63,1	0,06	51,9-73,5
24 hour urinary excretion	ml/min/kg	0,94	1,84	0,66-1,60
Serum clearance	%	56	0,07	39-67
Bioavailability				

(References: 10, 14)

10 MULTIPLE ACTIVE PHARMACEUTICAL INGREDIENTS:

Not applicable to this product

11 REGISTRATION STATUS IN OTHER COUNTRIES:

Country	Date of registration
U.S.A.	25-07-1986
U.K.	10-05-1985
Australia	04-02-1985

12 PROPOSED SCHEDULING STATUS:

S4
(Similar compounds have been allocated to S4 by Council, in the past).

13 LIST OF KEY REFERENCES:

1. James X. Pharmacology of rosalone. Br Med J 1984; 91:640-645
2. Etc.
3. Etc.
4. Scott et al. Rosalone in congestive heart failure: a double blind trial vs. digoxin. S Afr Med J 1985; 68: 201-205
5. "Side effects and ADR's of rosalone" – Rosepharm Labs, Report R&D 534, 1984

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