1C-1

APPLICANT/PHCR:	*CIPLA-MEDPRO (PTY) LTD*	*DOSAGE FORM AND STRENGTH:*	*CAPSULE 100 mg DANOZOL PER CAPSULE*
PRODUCT PROPRIETARY NAME :	*DANOGEN 100*		

2006 -01- 11

PART 1C LABELLING

a) Package insert

The under-mentioned information with regard to this medicine shall appear on the package insert. The information shall be presented in the format stipulated, provided that the Council may authorise any deviation from such information or such format (refer to Regulation 9 of the Act).

1 Scheduling status
2 Proprietary name and dosage form
3 Composition
4 Pharmacological classification
5 Pharmacological action
(Pharmacokinetics, pharmacodynamics and summary of clinical studies, where applicable)
6 Indications
7 Contra-indications
8 Warnings
9 Interactions
10 Pregnancy and lactation
11 Dosage and directions for use
12 Side effects and special precautions
13 Known symptoms of overdosage and particulars of its treatment
14 Identification
15 Presentation
16 Storage instructions
17 Registration number
18 Name and business address of the holder of the certificate of registration
19 Date of publication of the package insert

APPLICANT/PHCR:	*CIPLA-MEDPRO (PTY) LTD*	*DOSAGE FORM*	*CAPSULE*
PRODUCT		*AND STRENGTH:*	*100 mg DANOZOL PER*
PROPRIETARY NAME :	*DANOGEN 100*		*CAPSULE*

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PROPOSED PACKAGE INSERT FOR:

DANOGEN-50

DANOGEN-100

DANOGEN-200

2006 -01- 11

SCHEDULING STATUS:

S4

PROPRIETARY NAME(and dosage form)

DANOGEN-50 (Capsules)

DANOGEN-100 (Capsules)

DANOGEN-200 (Capsules)

COMPOSITION

Each Danogen - 50 capsule contains 50 mg of danazol

Each Danogen -100 capsule contains 100 mg of danazol

Each Danogen -200 capsule contains 200 mg of danazol

PHARMACOLOGICAL CLASSIFICATION

A.21.12. Hormone inhibitors.

PHARMACOLOGICAL ACTIONS

By suppressing the pituitary-ovarian axis, danazol inhibits the output of pituitary gonadotropins. Both the pre-ovulatory surge of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) are suppressed and therefore ovarian estrogen production is reduced. In the treatment of patients suffering from endometriosis, this action causes the normal and ectopic endometrial tissues becoming inactive and atrophic. Depending on the dosage used, anovulation and associated amenorrhea will occur after one or two menstrual cycles. In the treatment of fibrocystic breast disease, the pharmacological action may be related to the suppression of estrogenic stimulation and the resulting decreased ovarian production of estrogen.

APPLICANT/PHCR:	*CIPLA-MEDPRO (PTY) LTD*	*DOSAGE FORM*	*CAPSULE*
PRODUCT PROPRIETARY NAME :	*DANOGEN 100*	*AND STRENGTH:*	*100 mg DANOZOL PER CAPSULE*

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INDICATIONS

DANOGEN is indicated for the treatment of the following:

- Endometriosis
- Severe cyclic breast pain and nodularity.
- For the prophylactic treatment of hereditary angioneurotic oedema, (cutaneous, abdominal and laryngeal) in both males and females.

CONTRA-INDICATIONS

DANOGEN is contra-indicated in the following:

- Pregnant women as danazol may have androgenic effect on the female fetus.
- Nursing mothers as it may have androgenic effect in the infant, both male (possible precocious sexual development) and female (virilization).
- Patient suffering from thrombo-embolic disorders.
- Patients with severe hepatic, cardiac or kidney dysfunction.
- Hypersensitivity to anabolic steroids, androgens and danazol.
- Porphyria.

WARNINGS:

Therapy should begin on the first day of the menstrual cycle or after pregnancy has been excluded. If a patient should become pregnant during treatment, the administration of **DANOGEN** should be discontinued immediately because of the possible androgenic effect on the fetus.

INTERACTIONS;

Anticoagulants, coumarin or indanedione-derivative:

Concurrent use with **DANOGEN** may enhance effects of anticoagulants because of decreased hepatic synthesis of procoagulant factors, and may cause bleeding.

Antidiabetic agents, oral or Insulin:

DANOGEN may increase blood glucose concentration and resistance to insulin due to changes in the metabolism of carbohydrates; dosage adjustment of the antidiabetic agent or insulin maybe necessary.

Carbamazepine:

Concurrent use may cause inhibition of carbamazepine metabolism, resulting in increased plasma concentrations and toxicity.

Cyclosporine or Tacrolimus:

DANOGEN may increase plasma concentrations of cyclosporine and tacrolimus, and may increase the risk of nephrotoxicity.

Glucagons:

DANOGEN may increase the plasma concentrations of glucagon.

PREGNANCY AND LACTATION:

Use of **DANOGEN** during pregnancy and lactation is not recommended, as safety and efficacy has not been established **(see CONTRAINDICATIONS).**

DOSAGE AND DIRECTIONS FOR USE:

For woman:	Start treatment on day 1 of the menstrual cycle or after pregnancy has been excluded.
Endometriosis:	
For mild cases:	200 to 400 mg daily, divided into two doses.
Moderate to severe cases:	800 mg daily, divided into two doses.
Maintenance dose:	Adjust according to the response. Do not exceed the maximum dose of 800 mg daily. Treatment should last for at least 3 to 6 months. If necessary therapy may be continued for up to 9 months. Treatment may be re-instituted if symptoms recur after the termination of therapy.

Cyclical breast pain and nodularity:

200 mg daily, (100 mg twice daily), for a maximum recommended period of 3 months.

Hereditary angioneurotic oedema:

Initial adult dose of 400 mg daily.

After a 2 month attack-free period, the dosage should be reduced and individualised to the lowest effective dose.

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Paediatrics:

Caution is recommended in children and adolescent being treated for hereditary angio oedema, because of possible androgenic effects and premature epiphyseal closure.

Geriatrics:

No information is available on the effect of danazol in geriatric patients. In male patients there may be an increased risk of prostatic hypertrophy or prostatic carcinoma.

SIDE EFFECTS AND SPECIAL PRECAUTIONS:

Side-effects:

Adverse effects are mainly androgenic and dose related and may include the following:

Body as a whole:

Less Frequent: Alopecia, backache, deepening of the voice.

Gastrointestinal System Disorders:

Frequent: Gastro-intestinal disturbances.

Cardiovascular System Disorders:

Frequent: Hypertension, intracranial hypertension, tachycardia.

Haematological and Lymphatic System Disorders:

Frequent: Increased or decreased blood count.

Metabolic and nutritional:

Frequent: Hyper-glucagonaemia, abnormal glucose tolerance, decreased serum high-density-lipoprotein cholesterol, increased serum low-density-lipoprotein cholesterol, cholestatic jaundice, mild hirsutism, weight gain.

Musculoskeletal System Disorders:

Less Frequent: Muscle cramps and swelling of feet and lower legs, fatigue.

Central nervous system:

Frequent: Dizziness, depression, headache, tremor, sleep disorders, nervousness.

Skin and appendages:

Frequent: Acne, oily skin or hair, skin rash.

Special senses:

Frequent: Visual disturbances.

Urogenital System Disorders:

Frequent: Decreased breast size, spotting, irregular menstrual periods, breakthrough bleeding and weight gain Amenorrhoea, sweating, hot flushes, vaginitis, changes in libido and emotional lability have been reported, occasional clitoral hypertrophy, testicular atrophy, azoospermia.

Hepatic System Disorders:

Less Frequent: Elevation of liver-function tests.

Special precautions:

The use of **DANOGEN** may cause some degree of fluid retention. It is therefore advisable that **DANOGEN** be used with caution in conditions that are adversely affected by fluid retention. This may include conditions such as migraine, epilepsy, cardiac and renal diseases. Care should be used in patients with a history of thrombosis. Care should be exercised in patients with hepatic impairment. As **DANOGEN** may interfere with the control of diabetic patients due to the possible impairment of glucose tolerance, special care should be taken when prescribing **DANOGEN** to such patients. **DANOGEN** may enhance the effect of anticoagulants such as coumarin and indandione derivates and this may cause bleeding. The plasma concentration of cyclosporine may be increased by **DANOGEN** and this may lead to an increased risk of nephrotoxicity. It may be necessary to adjust the dosage of anti-epileptic medication. **DANOGEN** appears to reduce the maintenance requirement of alfacalcicol therapy in

patients treated for hypoparathyroidism. The action of **DANOGEN** may be modified by the concurrent use of oestrogens and progesterones. It is therefore advisable to use non-hormonal contraceptives.

Possible photosensitivity reactions may be observed. Caution is advised during exposure to sun or when using a sunlamp. It is recommended that the following tests be done at periodic intervals: Hepatic function tests, semen volume and viscosity tests as well as sperm count and mobility tests, especially in adolescents. To rule out carcinoma, mammography or biopsy of cysts, are advised before treatment with **DANOGEN** is started, and are also recommended during treatment if nodules persist or become enlarged.

KNOWN SYMPTOMS OF OVERDOSAGE AND TREATMENT:

See 'Side -Effects'. Treatment is supportive and symptomatic.

IDENTIFICATION:

DANOGEN - 50: Dark green coloured oblong hard gelatin capsules with 'DGN'/50 printed straight in white on both halves. Capsule size 2. The capsule is filled with off-white to pale yellow powder.

DANOGEN - 100: White coloured oblong hard gelatin capsules with 'DGN'/100 printed straight in white on both halves. Capsule size 2. The capsule is filled with off-white to pale yellow powder.

DANOGEN - 200: Scarlet red coloured oblong hard gelatin capsules with 'DGN'/200 printed straight in white on both halves. Capsule size 1 The capsule is filled with off-white to pale yellow powder.

PRESENTATION:

Blister pack with 10 capsules packed in 60's (6 x 10 Capsules).

STORAGE INSTRUCTIONS:

Store in tight, light resistant containers below 25°C.

KEEP OUT OF REACH OF CHILDREN

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APPLICANT/PHCR:	*CIPLA-MEDPRO (PTY) LTD*	*DOSAGE FORM AND STRENGTH:*	*CAPSULE 100 mg DANOZOL PER CAPSULE*
PRODUCT PROPRIETARY NAME :	*DANOGEN 100*		

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REGISTRATION NUMBER:

Danogen-50:	340108
Danogen-100:	340109
Danogen-200:	340110

NAME AND ADDRESS OF THE PROSPECTIVE HOLDER OF THE CERTIFICATE OF REGISTRATION:

Cipla-Medpro (Pty) Ltd

Rosen Height

Pasita Street

Rosen park

7530

DATE OF PUBLICATION OF THE PACKAGE INSERT:

APPLICANT/PHCR: *CIPLA-MEDPRO (PTY)LTD* *DOSAGE FORM* *CAPSULES*
PRODUCT *AND STRENGTH:* *100 mg Danazol per capsule*
PROPRIETARY NAME: *DANOGEN 100*

1C-8(a)

VOUBILJET

DANOGEN - 50
DANOGEN - 100
DANOGEN - 200

2006 -01- 11

SKEDULERINGSTATUS:
S5

EIENDOMSNAAM (en doseervorm):
DANOGEN-50 (Kapsules)
DANOGEN-100 (Kapsules)
DANOGEN-200 (Kapsules)

SAMESTELLING:
Danasol (17 alfa - pregna - 2,4 - dieen - 20 - ino (2,3-d) isoksasol - 17 - ol).
Elke DANOGEN-50 kapsule bevat 50mg danasol.
Elke DANOGEN-100 kapsule bevat 100mg danasol.
Elke DANOGEN-200 kapsule bevat 200mg danasol.

FARMAKOLOGIESE KLASSIFIKASIE:
A.21.12. Hormoon inhibeerders.

FARMAKOLOGIESE WERKING:
Deur die onderdrukking van die hipofiseale - ovariële as, inhibeer danasol die vrystelling van pituïtêre gonadotropiene. Beide die pre-ovulatoriese styging van folikelstimulerende hormoon (FSH) en luteïeniserende hormoon (LH) word onderdruk en derhalwe word ovariële estrogeenproduksie verminder. Tydens die behandeling van pasiënte met endometriose, veroorsaak hierdie werking dat normale en ektopiese endometriële weefsels onaktief en atrofies word. Afhangende van die dosis wat gebruik word, sal anovulasie en gepaardgaande amenorree voorkom na een of twee menstruele siklusse. Met die behandeling van fibrosistiese borssiekte, kan die farmakologiese werking verband hou met die onderdrukking van estrogeniese stimulasie as gevolg van verminderde ovariële produksie van estrogeen.

INDIKASIES:
DANOGEN is aangedui vir die behandeling van die volgende:
- Endometriose.
- Erge sikliese borspyn en -nodulariteit.
- Vir die profilaktiese behandeling van oorerflike angioneurotiese edeem (kutane, abdominale en laringeale), in beide mans en vrouens.

KONTRA-INDIKASIES:
DANOGEN is teenaangedui tydens swangerskap aangesien danasol androgeniese effekte in die vroulike fetus kan veroorsaak.
Die gebruik van DANOGEN tydens borsvoeding word nie aanbeveel nie weens die androgeniese effek op die suigeling, beide manlik (moontlike vroeë seksuele ontwikkeling) en vroulik (virilisasie).
DANOGEN behoort nie voorgeskryf te word vir pasiënte met trombo-emboliese verskynsels nie.
DANOGEN behoort vermy te word in pasiënte met erge lewer-, kardiale- of nierdisfunksie.
Hipersensitiwiteit vir anaboliese steroïede, androgene en danasol.
DANOGEN word as onveilig beskou in porfiriese pasiënte.

APPLICANT/PHCR:	*CIPLA-MEDPRO (PTY)LTD*	*DOSAGE FORM*	*CAPSULES*
PRODUCT		*AND STRENGTH:*	*100 mg Danazol per capsule*
PROPRIETARY NAME:	*DANOGEN 100*		

1C-8(b)

WAARSKUWINGS:

Terapie moet begin word op die eerste dag van die menstruele siklus of nadat swangerskap uitgeskakel is.

Indien 'n pasiënt swanger sou raak tydens behandeling, moet die toediening van DANOGEN dadelik gestaak word weens die moontlike androgeniese effek op die fetus.

DOSIS EN GEBRUIKSAANWYSINGS:

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In vrouens:	Begin behandeling op dag 1 van die menstruele siklus of nadat swangerskap uitgeskakel is.
Endometriose:	
Vir ligte gevalle:	200 tot 400mg daagliks, verdeel in twee dosisse.
Matige tot erge gevalle:	800mg daagliks, verdeel in twee dosisse.
Instandhoudingsdosis:	Pas aan volgens die respons. Moet nie die maksimum dosis van 800mg per dag oorskry nie. In sommige pasiënte kan dit moontlik wees om die instandhoudingsdosis te verminder sodra 'n bevredigende respons verkry is. Behandeling moet vir ten minste 3 tot 6 maande volgehou word. Indien nodig kan behandeling vir 9 maande voortgaan. Behandeling kan heringestel word indien simptome terugkeer na staking van terapie.

Dismenorree en pelviese pyn word gewoonlik verlig binne die eerste paar weke van behandeling.
Weens die omkeerbaarheid van die werking van DANOGEN, sal ovulasie en voorspelbare sikliese bloeding gewoonlik terugkeer binne 60 to 90 dae na staking van die behandeling.

Sikliese borspyn en -nodulariteit:	200mg daagliks (100mg twee maal 'n dag), vir 'n maksimum aanbevole tydperk van 3 maande.
Oorerflike angioneurotiese edeem:	Aanvanklike volwasse dosis van 400mg daagliks. Na 'n 2 maande aanval-vry periode, moet die dosis verminder en geïndividualiseer word tot die laagste effektiewe dosis.
Pediatrie:	Omsigtigheid word aanbeveel in kinders en jeugdiges wat behandel word vir oorerflike angioedeem, weens die moontlike androgeniese effekte en premature epifiseale sluiting.
Geriatrie:	Daar is geen informasie beskikbaar oor die effekte van danasol in bejaarde pasiënte nie. In manlike pasiënte kan daar 'n verhoogde risiko van prostatiese hipertrofie of prostaatkarsinoom wees.

NEWE-EFFEKTE EN SPESIALE VOORSORGMAATREËLS:

Newe-effekte:

Ongunstige effekte is hoofsaaklik androgenies en dosisafhanklik en kan die volgende insluit:

In vrouens: Verminderde borsgrootte, vlekking ("spotting"), ongereelde menstruasies, deurbraakbloeding en gewigstoename. Amenorree, sweet, warm gloede, vaginitis, senuagtigheid, veranderinge in libido en emosionele labiliteit is voorheen gemeld.

In beide mans en vrouens: Aknee, olierige vel of hare, dieper stemtoon, enkele gevalle van klitorale hipertrofie en geringe hirsutisme kan voorkom. Spierkrampe en swelling van voete en onderbene is gemeld. Gastro-intestinale afwykings, duiseligheid, depressie, haarverlies, hoofpyn, rugpyn, tremor, verhoogde of verlaagde bloedtellings, hiperglukagonemie, abnormale glukose toleransie, verlaagde serum hoë digtheid lipoproteïen (HDL) cholesterol, verhoogde serum lae digtheid lipoproteïen (LDL) cholesterol, slaapsteurnisse, moegheid en styging van lewerfunksietoetse. Hipertensie en visiestoornisse is al gemeld. Intrakraniale hipertensie, cholestatiese geelsug, veluitslag en tagikardie. Met langtermyn behandeling is baie van hierdie effekte, soos die dieper stemtoon, onomkeerbaar.

In mans: Testikulêre atrofie en azoöspermie.

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APPLICANT/PHCR:	*CIPLA-MEDPRO (PTY)LTD*	*DOSAGE FORM*	*CAPSULES*
PRODUCT		*AND STRENGTH:*	*100 mg Danazol per capsule*
PROPRIETARY NAME:	*DANOGEN 100*		

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Spesiale voorsorgmaatreëls:
Die gebruik van danasol kan 'n sekere mate van vogretensie tot gevolg hê. Dit word dus aanbeveel dat DANOGEN met omsigtigheid gebruik word in toestande waar vogretensie 'n nadelige effek kan hê. Dit kan toestande, soos migraine, epilepsie, kardiale en renale siektes, insluit.
Wees ook versigtig in pasiënte met 'n geskiedenis van trombose en dié met lewerinkorting.
Aangesien danasol met die beheer van diabetiese pasiënte kan inmeng weens die moontlike effek op glukose toleransie, moet spesiale sorg gedra word met die voorskryf van DANOGEN aan sulke pasiënte.
Danasol kan die effek van antistolmiddels, soos koemarien en indandioon derivate, versterk, wat dan bloeding kan veroorsaak.
Die plasmakonsentrasie van siklosporien kan verhoog word deur danasol, wat dan kan lei tot 'n verhoogde risiko van nefrotoksisiteit.
Dit mag nodig wees om die dosis van anti-epileptiese medikasie aan te pas.
DANOGEN blyk die instandhoudingsbehoeftes van alfakalsidol terapie te verminder in pasiënte wat vir hipoparatiroïedisme behandel word.
Die werking van danasol kan gewysig word deur die gesamentlike gebruik met estrogene en progesterone. Die gebruik van nie-hormonale voorbehoedmiddels word dus aanbeveel.
Moontlike fotosensitiwiteitsreaksies kan waargeneem word. Omsigtigheid word aanbeveel tydens sonblootstelling of wanneer 'n sonlamp gebruik word.
Dit word aanbeveel dat die volgende toetse van tyd tot tyd gedoen word: lewerfunksietoetse, semenvolume en -viskositeitstoetse, asook spermtellings en motiliteitstoetse, veral in adolessente.
Om karsinoom uit te skakel, word mammografie of biopsie van siste aanbeveel voordat behandeling met danasol begin word. Dit word ook aanbeveel tydens behandeling indien nodules nie verdwyn nie, of groter word.

BEKENDE SIMPTOME VAN OORDOSERING EN BESONDERHEDE VAN DIE BEHANDELING DAARVAN:
Sien "Newe - effekte".
Behandeling is simptomaties en ondersteunend.

IDENTIFIKASIE:

DANOGEN-50:	Donkergroenkleurige langwerpige harde gelatien kapsules met "DGN 50" reguit gedruk in wit op beide helftes. Kapsule groottte 2. Die kapsule is gevul met 'n naaswit tot liggeel poeier.
DANOGEN-100:	Witkleurige langwerpige harde gelatien kapsules met "DGN 100" reguit gedruk in wit op beide helftes. Kapsule grootte 2. Die kapsule is gevul met 'n naaswit tot liggeel poeier.
DANOGEN-200:	Helderrooikleurige langwerpige harde gelatien kapsules met "DGN 200" reguit gedruk in wit op beide helftes. Kapsule grootte 1. Die kapsule is gevul met 'n naaswit tot liggeel poeier.

AANBIEDING:
Stulpverpakte stroke met 10 kapsules, verpak in 60's (6 x 10 kapsules).

BERGINGSINSTRUKSIES:
Berg in digte, ligweerstandige houers, benede 25°C.
HOU BUITE BEREIK VAN KINDERS.

REGISTRASIENOMMERS:
DANOGEN-50: 34/21.12/0108
DANOGEN-100: 34/21.12/0109
DANOGEN-200: 34/21.12/0110

2006 -01- 11

APPLICANT/PHCR:	*CIPLA-MEDPRO (PTY)LTD*	*DOSAGE FORM AND STRENGTH:*	*CAPSULES*
PRODUCT PROPRIETARY NAME:	*DANOGEN 100*		*100 mg Danazol per capsule*

1C-8(d)

NAAM EN BESIGHEIDSADRES VAN DIE APPLIKANT:
CIPLA MEDPRO (Edms) Bpk
Rosen Heights
Pasitastraat
Rosen Park
Bellville, 7530

DATUM VAN PUBLIKASIE VAN HIERDIE VOUBILJET:
Mei 2001