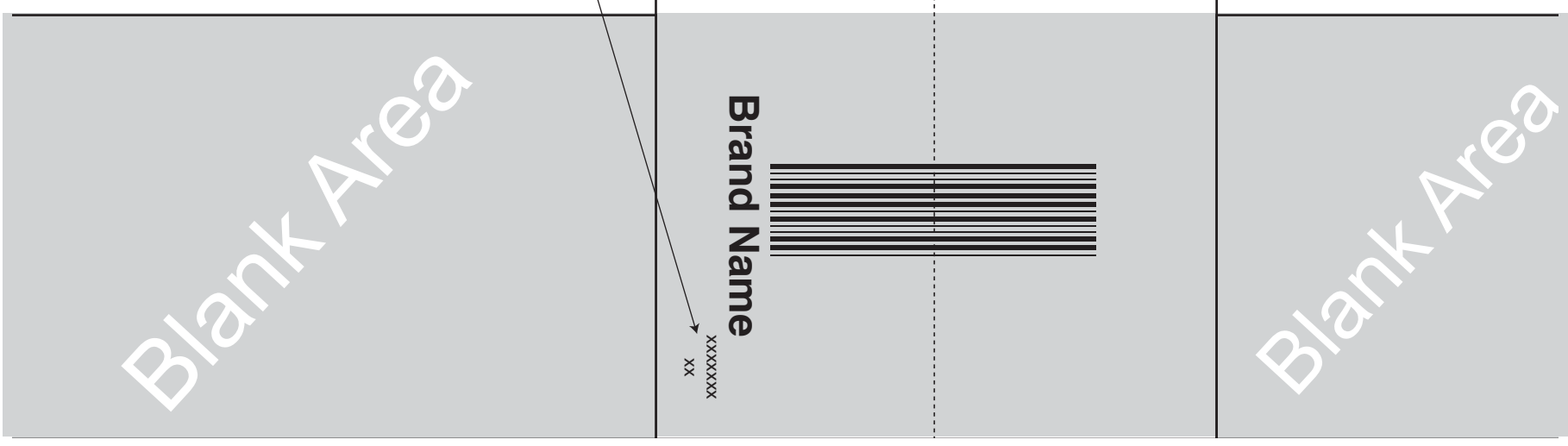


SCHEDULING STATUS: S4

PROPRIETARY NAME AND DOSAGE FORM:

FERTAB (TABLETS)

COMPOSITION:

Each tablet contains 50 mg clomiphene citrate.

Contains sugar:
Lactose monohydrate 119,138 mg/tablet. Sucrose 45,0 mg/tablet.

PHARMACOLOGICAL CLASSIFICATION:

A 18.8 Ovulation controlling agents

PHARMACOLOGICAL ACTION:

Pharmacodynamic properties
Clomiphene citrate is a triarylethylene compound. It is a non-steroidal agent which stimulates ovulation in a high percentage of appropriately selected anovulatory women.

Pharmacokinetic properties
Orally administered ^{14}C labelled clomiphene citrate was readily absorbed when administered to humans. Cumulative excretion of the ^{14}C label by way of urine and faeces averaged about 50 % of the oral dose after 5 days in 6 subjects, with mean urinary excretion of 7,8 % and mean faecal excretion of 42,4 %. A mean rate of excretion of 0,73 % per day of the ^{14}C dose after 31 days to 35 days and 0,45 % per day of the ^{14}C dose after 42 days to 45 days was seen in faecal and urine samples collected from 6 subjects for 14 to 53 days after clomiphene citrate ^{14}C administration. The remaining drug/metabolites may be slowly excreted from a sequestered enterohepatic recirculation pool.

INDICATIONS:

FERTAB is indicated in the treatment of anovulatory infertility.

CONTRAINDICATIONS:
Hypersensitivity to clomiphene citrate or to any of the other ingredients of **FERTAB**

- Pregnancy
- Liver disease or a history of liver dysfunction
- Pituitary failure
- Endometrial carcinoma or ovarian cysts (other than polycystic ovary)
- Abnormal uterine bleeding
- Pre-existing mental depression
- Thrombophlebitis

WARNINGS AND SPECIAL PRECAUTIONS:

To avoid inadvertent **FERTAB** administration during early pregnancy, the basal body temperature should be recorded throughout all treatment cycles, and the patient should be carefully observed to determine whether ovulation occurs. If the basal temperature following **FERTAB** is biphasic and is not followed by menses, the patient should be re-examined carefully and should have a pregnancy test.

Careful evaluation and selection of patients and close attention to dosage instructions, contra-indications and side-effects are mandatory. Since **FERTAB** stimulates the ovaries it should not be given in the presence of an ovarian cyst (including endometriosis involving the ovary), except polycystic ovary, as further enlargement of the cyst may occur. Pelvic examination is therefore necessary prior to start of and before each subsequent course of **FERTAB** treatment.

To minimise the hazard of the abnormal ovarian enlargement associated with **FERTAB** therapy the lowest dose consistent with expectation of good results should be used. The patient should be instructed to inform the medical practitioner of any abdominal or pelvic pain, weight gain, discomfort or distension after taking **FERTAB**. A patient who complains of abdominal or pelvic pain, discomfort or distension after taking **FERTAB** should be examined because of the possible presence of an ovarian cyst or other cause. If abnormal ovarian enlargement occurs, **FERTAB** should not be given until the ovaries have returned to pre-treatment size. The ovarian enlargement and cyst formation associated with **FERTAB** therapy may regress spontaneously within a few days or weeks after discontinuing treatment. Most of these patients should be managed conservatively. The dosage and duration of the next dose should be reduced.

At recommended dosage, the normal variation in ovarian size may be exaggerated.

Visual symptoms described usually as “blurring” or spots or flashes (scintillating scotomata), increase in incidence with increasing total dose and may disappear within a few days or weeks after treatment is discontinued. Ophthalmologically definable scotomata and retinal cell function (electroretinographic) changes may occur. If visual symptoms occur, **FERTAB** should be discontinued and a complete ophthalmological evaluation should be made. No further course of **FERTAB** should be administered.

Multiple pregnancies:
There is an increased chance of multiple pregnancies when conception occurs in relationship to **FERTAB** therapy. There is also an increased risk of ectopic pregnancy. The potential complications and hazards of multiple pregnancies should be discussed with the patient and her husband.

Pregnancy Wastages and Birth Anomalies:
Birth anomalies may occur in pregnancies associated with maternal clomiphene citrate ingestion (as contained in **FERTAB**).

Population based reports have been published on possible elevation of risk of Down’s Syndrome in ovulation induction cases and of increase in trisomy defects among spontaneously aborted foetuses from sub fertile women receiving ovulation inducing medicines.

Lactose intolerance: FERTAB contains lactose and should not be given to patients with rare hereditary problems, or a history of galactose intolerance, Lapp lactose deficiency or glucose-galactose malabsorption.

Effects on ability to drive and use machines: Patients should be warned that visual symptoms may render such activities as driving a car or operating machinery more hazardous than usual, particularly under conditions of variable lighting.

INTERACTIONS:

Interaction studies have not been conducted with clomiphene citrate

PREGNANCY AND LACTATION:

FERTAB is contraindicated during pregnancy. The patient should have a pregnancy test before a course of **FERTAB** therapy.

It is not known whether clomiphene citrate is excreted in human milk. **FERTAB** may reduce lactation.

DOSAGE AND DIRECTIONS FOR USE:

The recommended dose for the first course of **FERTAB** is 50 mg (1 tablet) daily for 5 days. Therapy may be started at any time in the patient who has had no recent uterine bleeding.
If progestin-induced bleeding is planned, or if spontaneous uterine bleeding occurs before therapy, the regimen of 50 mg daily for 5 days should be started on or about the fifth day of the cycle. When ovulation occurs at this dosage there is no advantage to increasing the dose in subsequent cycles of treatment.

If ovulation appears not to have occurred after the first course of therapy, a second course of 100 mg daily (two 50 mg tablets given as a single dose) for 5 days should be given. This course may be started as early as 30 days after the previous one. **Increase of the dosage or duration of therapy beyond 100 mg per day for 5 days should not be undertaken.**

The majority of patients who are going to respond will respond to the first course of therapy, and three courses should constitute an adequate therapeutic trial. If ovulatory menses did not yet occur, the diagnosis should be re-evaluated. Treatment beyond this is not recommended in the patient who does not exhibit evidence of ovulation.

Ovulation most often occurs from 6-12 days after a course of **FERTAB** thus the importance of properly timed coitus cannot be over-emphasised. For regularity of cyclic ovulatory response it is also important that each course of **FERTAB** be started on or about the fifth cycle day, once ovulation has been established.

FERTAB therapy is not effective in patients in whom primary pituitary or normal ovarian failure precludes the possibility of stimulating normal function. Some anovulatory patients who appear to respond to **FERTAB**, but either do not ovulate or whose luteal phases are so short that the opportunity to conceive is limited may benefit by having the course of **FERTAB** followed by injections of human chorionic gonadotrophin (HCG) at about the expected time of ovulation. Infertile patients with polycystic ovary syndrome who have not responded to wedge resection of the ovary may respond to **FERTAB**.

SIDE EFFECTS:

Side effects are dose related.

Reproductive system and breast disorders:
Frequent – Ovarian enlargement, vasomotor flushes, abdominal-pelvic discomfort

Less frequent – menorrhagia, intermenstrual spotting, ovarian hyperstimulation syndrome, breast tenderness, endometriosis, mastalgia, hydatiform mole formation

Instances of massive ovarian enlargement and rupture of a lutein cyst with haemoperitoneum have been reported.

Eye disorders:
Frequent – visual blurring

Less frequent – cataracts, optic neuritis

Gastrointestinal disorders:
Less frequent – nausea, vomiting, weight gain

Nervous system disorders:
Less frequent – increased nervous tension, fatigue, dizziness or light headedness, headache, syncope/fainting, neurologic impairment, speech disturbance, cerebrovascular accident, cerebral thrombosis, convulsions

Psychiatric disorders:
Less frequent – depression, insomnia, psychotic reactions including paranoid psychosis, disorientation

Ear and labyrinth disorders:
Less frequent – vertigo

Skin and subcutaneous tissue disorders:
Less frequent – skin reactions such as allergic rashes and urticaria, moderate reversible alopecia

Renal and urinary disorders:
Less frequent – increased urinary frequency

Hepato-biliary disorders:
Less frequent – abnormal liver function tests, jaundice

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

Acute overdosage of clomiphene citrate has not been reported. Signs and symptoms of intoxication, nausea, vomiting, vasomotor flushes, visual blurring or flashes, scotomata, ovarian enlargement with pelvic or abdominal pain. Severe hyperstimulation of ovary may be accompanied by weight gain and ascites. Maximal enlargement of the ovary may not occur until several days after discontinuation of the course of **FERTAB**. Female patients in reproductive age who have taken an overdose should be observed for 2 to 3 weeks for ovarian enlargement. Gastric lavage is recommended.

IDENTIFICATION:
Cream to slightly yellowish, circular, flat, bevel edged tablet having CT engraved on one side and central break line on the other side

PRESENTATION:
Unit carton containing 10 tablets in clear PVC/silver aluminium blister strips.

STORAGE INSTRUCTIONS:
Store at or below 30 °C in a dry place protected from light.

Do not remove the blisters from the unit carton until required for use.

KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBER:

44/18.8/1034

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

Gulf Drug Company (Pty) Ltd
22 Burnside Drive
Old Mill Industrial Park
Mount Edgecombe, 4300
www.gulfdrug.co.za

DATE OF PUBLICATION OF THIS PACKAGE INSERT:

09 June 2016

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SKEDULERINGSTATUS: S4

EIENDOMSNAAM EN DOSEERVORM:

FERTAB (Tablette)

SAMESTELLING:

Elke tablet bevat 50 mg klomifeensitraat.

Bevat suiker: Laktosemonohidraat 119,138 mg/tablet. Sukrose: 45,0 mg/tablet.

FARMAKOLOGIESE KLASSIFIKASIE

A 18.8 Ovulasiebeheermiddel

FARMAKOLOGIESE WERKING:

Farmakodinamiese eienskappe
Klomifeensitraat is ‘n triarieletileenverbinding. Dit is ‘n nie-steroïd middel wat ovulasie stimuleer in ‘n hoë persentasie toepaslik geselekteerde anovulatoriese vroue.

Farmakokinetiese eienskappe
^{14}C-gemerkte klomifeensitraat wat mondeliks toegedien word, is geredelik na toediening deur mense geabsorbeer. Die kumulatiewe uitskeiding van die ^{14}C-merking deur die uriene en ontlasting was na 5 dae in 6 proefpersone gemiddeld 50 % van die mondelikse dosis, met ‘n gemiddelde urienuitskeiding van 7,8 % en ‘n gemiddelde uitskeiding deur die ontlasting van 42,4 %. ‘n Gemiddelde uitskeidingskoers van die ^{14}C-dosis van 0,73 % per dag na 31 tot 35 dae en 0,45 % per dag na 42 tot 45 dae het voorgekom in ontlasting- en urienmonsters van 6 proefpersone wat vir 14 tot 53 dae na toediening van klomifeensitraat-^{14}C geneem is. Die oorblywende geneesmiddel/metaboliete mag stadig uitgeskei word uit ‘n geïsoleerde enterohepatiese hersikuleringspoel.

INDIKASIES:

FERTAB word aangedui vir die behandeling van anovulatoriese onvrugbaarheid.

KONTRA-INDIKASIES:

Hipersensitiwiteit vir klomifeensitraat of vir enige van die ander bestanddele van **FERTAB**

- Swangerskap
- Lewersiekte of ‘n geskiedenis van lewerdisfunksie
- Pituïtêre versaking
- Endometriese karsinoom of siste van die eierstokke (met die uitsondering van polisistiese eierstokke)
- Abnormale bloeding van die uterus
- Bestaande depressie
- Tromboflebitis

WAARSKUWINGS EN SPESIALE VOORSORGMAATREËLS:

Om te voorkom dat **FERTAB** per ongeluk tydens vroeë swangerskap toegedien word, moet die basale liggaamstemperatuur dwarsdeur al die behandelingsiklusse aangeteken word, en die pasiënt moet noukeurig waargeneem word om te bepaal of ovulasie plaasvind. Indien die basale temperatuur na **FERTAB** bifasies is en nie deur menstruasie gevolg word nie, moet die pasiënt noukeurig herondersoek word.

Dit is verpligtend om die pasiënte versigtig te evalueer en te keur en noukeurig aandag te gee aan die doseringsinstruksies, kontra-indikasies en newe-effekte. Aangesien **FERTAB** die eierstokke stimuleer, moet dit nie toegedien word waar siste van die eierstokke (met inbegrip van endometriose wat die eierstokke insluit) voorkom nie, buiten in die geval van polisistiese eierstokke, aangesien die sists verder kan vergroot. ‘n Bekkenonderoek moet dus gedoen word voordat daar met die behandeling met **FERTAB** begin word, en voor die toediening van enige daaropvolgende kursus.

Om die gevaar van abnormale vergroting van die eierstokke wat verband hou met **FERTAB**-terapie te verminder, moet die laagste moontlike dosering gebruik word om die verwagte goeie resultate te verkry. Die pasiënt moet in kennis gestel word om die geneesheer in kennis te stel van enige abdominale of bekkenpyn, gewigstoename, ongemak of distensie na gebruik van **FERTAB**. ‘n Pasiënt wat kla oor abdominale of bekkenpyn, ongemak of distensie nadat **FERTAB** gebruik is, moet ondersoek word vir ‘n moontlike eierstoksist of ‘n ander oorsaak. Indien abnormale vergroting van die eierstokke voorkom, moet **FERTAB** nie toegedien word voordat die eierstokke nie weer die voorbehandelingsgrootte bereik het nie. Die vergroting van die eierstokke en vorming van siste wat verband hou met **FERTAB**-terapie kan binne ‘n paar dae of weke na die staking van behandeling spontaan afneem. Die meeste van hierdie pasiënte behoort konserwatief bestuur te word. Die dosis en die duur van die volgende dosering moet verminder word.

Die gewone verskil in eierstokgrootte kan teen die aanbevole dosis vergroot word.

Visuele simptome wat beskryf word as “dowwe sig” of kolle of flitse (flikkerende skotomata) kom meer voor na mate die totale dosis toeneem en kan binne ‘n paar dae of weke na die staking van behandeling, verdwyn. Optalmologies definieërbare skotomata en veranderinge in die retinale selfunksie (elektroretinografies) kan voorkom. Behandeling met **FERTAB** moet gestaak word en ‘n volledige optalmologiese evaluering moet gedoen word indien visuele simptome voorkom. Geen verdere kursus **FERTAB** moet toegedien word nie.

Meervoudige swangerskappe:
Daar is ‘n groter moontlikheid van meervoudige swangerskappe wanneer bevrugting plaasvind met **FERTAB**- terapie. Daar is ook ‘n verhoogde risiko van ektopiese swangerskappe. Die potensiële komplikasies en gevare van meervoudige swangerskappe moet met die pasiënt en haar man bespreek word.

Swangerskapverkwisting en geboorte-abnormaliteite:
Geboorte-abnormaliteite kan voorkom in swangerskappe wat verband hou met die inname van klomifeensitraat (soos in **FERTAB**) deur die moeder.

Bevolkingsgebaseerde verslae oor die moontlike verhoogde risiko van Downsindroom in ovulasie-geïnduseerde gevalle en ‘n toename in trisomie-defekte in spontaangeaborteerde fetusse van sub-vrugbare vroue wat ovulasie-induseringsmiddels ontvang, is gepubliseer.

Laktose-intoleransie: FERTAB bevat laktose en moenie gegee word aan pasiënte met seldsame oorerflike probleme of ‘n geskiedenis van galaktose-intoleransie, Lapp-laktosetekort of glukose-galaktose-wanabsorpsie nie.

Uitwerking op die vermoë om te bestuur en masjinerie te gebruik: Pasiënte moet gewaarsku word dat visuele simptome aktiwiteite soos motorbestuur en masjiengebruik gevaarliker as gewoonlik kan maak, veral in wisselende ligtoestande.

INTERAKSIES:

Daar is nie interaksiestudies is met klomifeensitraat gedoen nie.

SWANGERSKAP EN BORSVOEDING:

FERTAB word teenaangedui tydens swangerskap. Die pasiënt moet ‘n swangerskaptoets doen voordat daar met ‘n kursus **FERTAB**-terapie begin word.

Dit is onbekend of klomifeensitraat in borsmelk uitgeskei word. **FERTAB** kan laktasie verminder.

DOSERING EN GEBRUIKSAANWYSINGS:

Die aanbevole dosis vir die eerste kursus **FERTAB** is 50 mg (1 tablet) daagliks vir 5 dae. Terapie kan ter enige tyd begin word in pasiënte wat nie onlangs uterusbloeding ondervind het nie. Indien progestiengeïnduseerde bloeding beplan word, of indien spontane uterusbloeding voor die aanvang van terapie voorkom, moet die doseringsvoorskrif van 50 mg daagliks vir 5 dae op of rondom die vyfde dag van die siklus begin word. Indien ovulasie teen hierdie dosis plaasvind, sal daar nie baat gevind word om die dosis in daaropvolgende behandelingsiklusse te verhoog nie.

Indien ovulasie skynbaar nie na die eerste kursus terapie plaasgevind het nie, moet ‘n tweede kursus van 100 mg daagliks (twee 50-mg-tablette as ‘n enkeldosis) vir 5 dae gegee word. Daar kan so gou as 30 dae na die vorige kursus met hierdie kursus begin word. **Die dosis en die duur van die terapie moet nie verhoog word tot bo 100 mg per dag vir 5 dae nie.**

Die meeste pasiënte wat gaan reageer, sal op die eerste kursus van die terapie reageer, en drie kursusse behoort ‘n voldoende terapeutiese proef te wees. Indien ovulêre menstruasie nog nie plaasgevind het nie, moet die diagnose heroorweeg word. Daar word nie aanbeveel dat behandeling voortgesit word in pasiënte wat nie tekens van ovulasie toon nie.

Ovulasie vind meesal 6-12 dae na voltooiing van ‘n kursus **FERTAB** plaas en dus kan die belangrikheid van die tydsberekening vir koïtus nie oorbeklemtoon word nie. Vir ‘n gereelde sikliese ovulasierespons, is dit ook belangrik dat daar op of rondom die vyfde dag van die siklus begin moet word met ‘n kursus **FERTAB** nadat ovulasie gevestig is.

FERTAB-terapie is nie effektief in pasiënte by wie primêre pituïtêre of normale eierstokfaling die moontlikheid om normale funksionering te stimuleer, verhinder nie. Sommige anovulatoriese pasiënte wat skynbaar op **FERTAB** reageer maar wat òf nie ovuleer nie òf wie se luteale fases so kort is dat die geleentheid vir bevrugting beperk is, kan baat daarby om die kursus **FERTAB** op te volg met inspuitings van menslike korioniese gonadotropien om en by die verwagte ovulasietyd. Onvrugbare pasïente met polisistiese-eierstoksindroom wat nie gereageer het op wigherseksie van die eierstok nie, mag reageer op **FERTAB**.

NEWE-EFFEKTE:

Newe-effekte hou verband met dosering

Voorplantingstelsel-en borssteurnisse:
Dikwels – vergroting van die eierstokke, vasomotoriese gloede, abdominale-bekken ongemak

Minder dikwels – Verlengde of vermeerderde bloeding tydens menstruasie, tussenmenstruasie vlekking, ovariesehiperstimulasiesindroom, gevoelige borste, endometriose, mastalgie, hidatievorme moesievorming

Gevalle van massiewe eierstokvergroting en gebarste luteïnsiste met hemoperitoneum is aangemeld

Oogsteurnisse:
Dikwels- dowwe visie

Minder dikwels – katarakke, optiese neuritis

Spysverteringsteurnisse:
Minder dikwels – naarheid, braking, gewigstoename

Senustelselsteurnisse:
Minder dikwels – verhoogde senuspanning, moegheid, duiseligheid of lighoofdigheid, hoofpyn, sinkopee/floutes, neurologiese belemmering, spraakversteuring, serebrovaksulêre insidente, serebrale trombose, konvulsies

Psigiatriese steurnisse:
Minder dikwels – depressie, slapeloosheid, psigotiese reaksies insluitende paranoïse psigose, disorïentering

Oor- en labarintsteurnisse:
Minder dikwels: vertigo

Vel- en subkutaneuse weefselsteurnisse:
Minder dikwels – velreaksies soos allergiese uitslag en urtikarie, matige omkeerbare alopesie

Nier- en uriensteurnisse:
Minder dikwels – verhoogde urineringsfrekwensie

Lewer-galsteurnisse:
Minder dikwels – abnormale lewerfunksietoetse, geelsug

BEKENDE SIMPTOME VAN OORDOSERING EN BESONDERHEDE VIR DIE BEHANDELING DAARVAN:

Akute oordosering van klomifeensitraat is nie aangemeld nie. Tekens en simptome van bedwelming, naarheid, braking, vasomotoriese gloede, dowwe visie of flitse, skotomata, vergrote eierstokke met bekken- of abdominale pyn. Ernstige hiperstimulasie van die eierstokke kan gepaard gaan met gewigstoename en askites. Die maksimale vergroting van die eierstokke mag plaasvind nadat die kursus **FERTAB** reeds vir etlike dae gestaak is. Vroulike pasiënte wat binne die reproduktiewe ouderdom val en wat ‘n oordosis geneem het, moet vir 2 tot 3 weke waargeneem word om te bepaal of die eierstokke vergroot is. Maagspoeling word aanbeveel.

IDENTIFIKASIE:

Roomkleurige tot ietwat gelerige ronde, plat afgeskuitste tablet met CT aan die eenkant gegraveer en ‘n middelbreeklyn aan die anderkant

AANBIEDING:

Eenheidkartonne wat 10 tablette in deursigtige PVC/silweraluminiumstulpstroke bevat

BERGINGSINSTRUKSIES:

Bewaar teen of benede 30 °C, in ’n droë plek beskerm teen lig.

Moenie die stulpe uit die eendheidskarton verwyder voordat dit gebruik moet word nie.

HOU BUITE BEREIK VAN KINDERS.

REGISTRASIENOMMER:

44/18.8/1034

NAAM EN BESIGHEIDSADRES VAN DIE HOUER VAN DIE SERTIFIKAAT VAN REGISTRASIE:

Gulf Drug Company (Pty) Ltd
22 Burnside Drive
Old Mill Industrial Park
Mount Edgecombe, 4300
www.gulfdrug.co.za

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