SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

OVESTIN CREAM

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Estriol 0.1% w/w (1mg estriol in 1g cream)
For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Vaginal cream
Homogeneous, smooth, white to nearly white mass of creamy consistency.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

For the treatment of vulvo-vaginal complaints related to estrogen deficiency.

4.2 Posology and method of administration

Ovestin cream is an estrogen-only product for intravaginal use.

One applicator-dose (applicator filled to the red mark) is 0.5g Ovestin cream containing 0.5 mg estriol.

Adults and Elderly

- Treatment of atrophic vaginitis
  For initiation and continuation of treatment of postmenopausal symptoms, the lowest effective dose for the shortest duration (see also section 4.4) should be used.
  The usual dose for atrophic vaginitis associated with the menopause is one applicator-dose per day for 2 to 3 weeks.
  As maintenance dosage, one applicator-dose twice a week is recommended.
  Medication should be discontinued every 2 to 3 months for a period of 4 weeks to assess the necessity for further treatment.
- Pre-surgery therapy
  One applicator-dose per day should begin 2 weeks before the operation.
- Post-surgery therapy

Following surgery a period of at least 2 weeks should be allowed before resuming therapy using one applicator-dose twice a week.

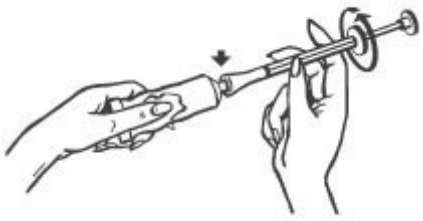
In women not taking HRT or women who switch from another continuous combined HRT product, treatment with Ovestin cream may be started on any day. Women who switch from cyclic HRT regimen should start Ovestin cream treatment one week after completion of the cycle.

Route of Administration
Ovestin cream is administered intravaginally by means of a calibrated applicator.

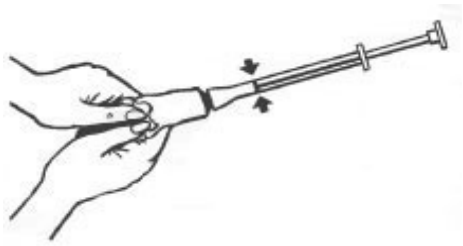
The following 'Instructions for Use' should be given to the patient and are included in the Patient Information Leaflet:
How to Apply the Cream
Use the applicator to apply the cream in the vagina. A good time to do this is before going to bed.

The applicator has a ring marked on the body. Fill the applicator up to the ring mark with Ovestin cream to get the correct dose.

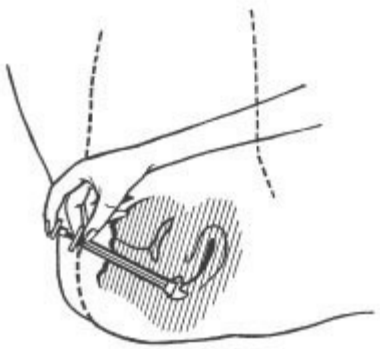
1. Remove the cap from the tube and turn it upside down. Then use the sharp point to open the tube.
2. Screw the end of the applicator onto the tube**.**



3. Squeeze the tube to fill the applicator with the cream up to the red ring mark (the plunger will stop at the ring mark).



4. Unscrew applicator from the tube and put the cap back on the tube.
5. To apply the cream, lie down, put the end of the applicator deep into the vagina and slowly push plunger all the way in until applicator is empty.



Cleaning the applicator
After use, pull the plunger out of the barrel. Wash the plunger and barrel in hand hot, soapy water. Do not use detergents. Rinse well with clean water afterwards.
DO NOT PUT THE APPLICATOR IN BOILING WATER.

A missed dose should be administered as soon as remembered, unless it is more than 12 hours overdue. In the latter case the missed dose should be skipped and the next dose should be administered at the normal time. Two doses should never be administered on the same day.

Cyclic administration of a progestagen to prevent endometrial stimulation is not necessary provided the daily dose does not exceed 1 applicator-dose (0.5 mg estriol) and this maximum dose is not used for more than several weeks (see section 4.4 Endometrial hyperplasia).

Children
There are no clinical trials to support the use in children.

4.3 Contraindications

- Known, past or suspected breast cancer;
- Known or suspected estrogen-dependent malignant tumours (e.g endometrial cancer);
- Undiagnosed genital bleeding;
- Untreated endometrial hyperplasia;
- Previous or current venous thromboembolism (deep venous thrombosis, pulmonary embolism);
- Known thrombophilic disorders (e.g. protein C, protein S, or antithrombin deficiency, see section 4.4);
- Active or recent arterial thromboembolic disease (e.g. angina, myocardial infarction);
- Acute liver disease, or a history of liver disease as long as liver function tests have failed to return to normal;
- Known hypersensitivity to the active substances or to any of the excipients listed in section 6.1;
- Porphyria.

4.4 Special warnings and precautions for use

For the treatment of postmenopausal symptoms, HRT should only be initiated for symptoms that adversely affect quality of life. In all cases, a careful appraisal of the risks and benefits should be undertaken at least annually and HRT should only be continued as long as the benefit outweighs the risk.

Medical examination/follow-up
Before initiating or reinstituting HRT, a complete personal and family medical history should be taken. Physical (including pelvic and breast) examination should be guided by this and by the contraindications and warnings for use. During treatment, periodic check-ups are recommended of a frequency and nature adapted to the individual woman. Women should be advised what changes in their breasts should be reported to their doctor or nurse. Investigations, including mammography, should be carried out in accordance with currently accepted screening practices, modified to the clinical needs of the individual.

In case of vaginal infections, these should be treated before therapy with Ovestin Cream is started.

Conditions which need supervision
If any of the following conditions are present, have occurred previously, and/or have been aggravated during pregnancy or previous hormone treatment, the patient should be closely supervised. It should be taken into account that these conditions may recur or be aggravated during treatment with Ovestin Cream, in particular:

- Leiomyoma (uterine fibroids) or endometriosis
- A history of, or risk factors for, thromboembolic disorders (see below)
- Risk factors for estrogen dependent tumours, e.g. 1st degree heredity for breast cancer
- Hypertension
- Liver disorders (e.g. liver adenoma)
- Diabetes mellitus with or without vascular involvement
- Cholelithiasis
- Migraine or (severe) headache
- Systemic lupus erythematosus.
- A history of endometrial hyperplasia (see below)
- Epilepsy
- Asthma
- Otosclerosis

Reasons for immediate withdrawal of therapy:
Therapy should be discontinued in case a contra-indication is discovered and in the following situations:

- Jaundice or deterioration in liver function
- Significant increase in blood pressure
- New onset of migraine-type headache
- Pregnancy

Endometrial hyperplasia

- The endometrial safety of long-term or repeated use of topical vaginal estrogens is uncertain. Therefore, if repeated, treatment should be reviewed at least annually, with special consideration given to any symptoms of endometrial hyperplasia or carcinoma
- In order to prevent endometrial stimulation, the daily dose should not exceed 1 application (0.5 mg estriol) nor should this maximum dose be used for longer than several weeks. One epidemiological study has shown that long-term treatment with low doses of oral estriol, but not vaginal estriol, may increase the risk for endometrial cancer. This risk increased with the duration of treatment and disappeared within one year after the treatment was terminated. The increased risk mainly concerned less invasive and highly differentiated tumors. Vaginal bleeding during medication should always be investigated. The patient should be informed to contact a doctor if vaginal bleeding occurs.
- If breakthrough bleeding or spotting appears at any time on therapy, the reason should be investigated which may include endometrial biopsy to exclude endometrial malignancy.
- Unopposed estrogen stimulation may lead to premalignant transformation in the residual foci of endometriosis. Therefore, caution is advised when using this product in women who have undergone hysterectomy because of endometriosis, especially if they are known to have residual endometriosis.

Breast cancer

- HRT may increase mammographic density. This may complicate the radiological detection of breast cancer. Clinical studies reported that the likelihood of developing increased mammographic density was lower in subjects treated with estriol than in subjects treated with other estrogens.
- A randomised placebo-controlled trial, the Women's Health Initiative study (WHI), and epidemiological studies, including the Million Women Study (MWS), have reported an increased risk of breast cancer in women taking estrogens, estrogen-progestagen combinations or tibolone for HRT for several years (see section 4.8). For all HRT, an excess risk becomes apparent within a few years of use and increases with duration of intake but returns to baseline within a few (at most five) years after stopping treatment.
- In the MWS, the relative risk of breast cancer with conjugated equine estrogens (CEE) or estradiol (E2) was greater when a progestagen was added, either sequentially or continuously, and regardless of type of progestagen. There was no evidence of a difference in risk between the different routes of administration.
- In the WHI study, the continuous combined conjugated equine estrogen and medroxyprogesterone acetate (CEE + MPA) product used was associated with breast cancers that were slightly larger in size and more frequently had local lymph node metastases compared to placebo. HRT, especially estrogen-progestagen combined treatment, increases the density

of mammographic images which may adversely affect the radiological detection of breast cancer.

Venous thromboembolism

- HRT is associated with a higher relative risk of developing venous thromboembolism (VTE), i.e. deep vein thrombosis or pulmonary embolism. One randomised controlled trial and epidemiological studies found a two- to threefold higher risk for users compared with non-users. For non-users it is estimated that the number of cases of VTE that will occur over a 5 year period is about 3 per 1000 women aged 50-59 years and 8 per 1000 women aged between 60-69 years. It is estimated that in healthy women who use HRT for 5 years, the number of additional cases of VTE over a 5 year period will be between 2 and 6 (best estimate = 4) per 1000 women aged 50-59 years and between 5 and 15 (best estimate = 9) per 1000 women aged 60-69 years. The occurrence of such an event is more likely in the first year of HRT than later (see section 4.8).
- Generally recognised risk factors for VTE include a personal history or family history, severe obesity (BMI > 30 kg/m^2), and systemic lupus erythematosus (SLE). There is no consensus about the possible role of varicose veins in VTE.
- Patients with a history of VTE or known thrombophilic states have an increased risk of VTE. HRT may add to this risk. Personal or strong family history of thromboembolism or recurrent spontaneous abortion should be investigated in order to exclude a thrombophilic predisposition. Until a thorough evaluation of thrombophilic factors has been made or anticoagulant treatment initiated, use of HRT in such patients should be viewed as contraindicated. Those women already on anticoagulant treatment require careful consideration of the benefit-risk of use of HRT.
- The risk of VTE may be temporarily increased with prolonged immobilization, major trauma or major surgery. As in all postoperative patients, scrupulous attention should be given to prophylactic measures to prevent VTE following surgery. Where prolonged immobilization is liable to follow elective surgery, particularly abdominal or orthopaedic surgery to the lower limbs, consideration should be given to temporarily stopping HRT 4 to 6 weeks earlier, if possible. Treatment should not be restarted until the woman is completely mobilized.
- If VTE develops after initiating therapy, the drug should be discontinued. Patients should be told to contact their doctors immediately when they are aware of a potential thromboembolic symptom (e.g., painful swelling of a leg, sudden pain in the chest, dyspnea).

Coronary artery disease (CAD)

- There is no evidence from randomized controlled trials of cardiovascular benefit with continuous combined conjugated estrogens and medroxyprogesterone acetate (MPA). Two large clinical trials (WHI and HERS i.e. Heart and Estrogen/progestin Replacement Study) showed a possible increased risk of cardiovascular morbidity in the first year of use and no overall benefit. For other HRT products there are only limited data from randomised controlled trials examining effects in cardiovascular

morbidity or mortality. Therefore, it is uncertain whether these findings also extend to other HRT products.

- One large randomised clinical trial (WHI-trial) found, as a secondary outcome, an increased risk of ischaemic stroke in healthy women during treatment with continuous combined conjugated estrogens and MPA. For women who do not use HRT, it is estimated that the number of cases of stroke that will occur over a 5 year period is about 3 per 1000 women aged 50-59 years and 11 per 1000 women aged 60-69 years. It is estimated that for women who use conjugated estrogens and MPA for 5 years, the number of additional cases will be between 0 and 3 (best estimate = 1) per 1000 users aged 50-59 years and between 1 and 9 (best estimate = 4) per 1000 users aged 60-69 years. It is unknown whether the increased risk also extends to other HRT products.

Concomitant use of Hepatitis C medications

- During clinical trials with the combination drug regimen ombitasvir hydrate/paritaprevir hydrate/ritonavir with or without dasabuvir, ALT elevations to greater than 5 times the upper limit of normal (ULN) were significantly more frequent in female subjects using ethinyl estradiol-containing medications. Women using estrogens other than ethinyl estradiol, such as estradiol, estriol and conjugated estrogens had a rate of ALT elevation similar to those not receiving any estrogens; however, due to the limited number of subjects taking these other estrogens, caution is warranted for co-administration with the combination drug regimen ombitasvir hydrate/paritaprevir hydrate/ritonavir with or without dasabuvir. (See section 4.5.)

Ovarian cancer

- Long-term (at least 5-10 years) use of estrogen-only HRT products in hysterectomised women has been associated with an increased risk of ovarian cancer in some epidemiological studies. It is uncertain whether long-term use of combined HRT confers a different risk than estrogen-only products.

Other conditions

- Estrogens may cause fluid retention, and therefore patients with cardiac or renal dysfunction should be carefully observed. Patients with terminal renal insufficiency should be closely observed, since it is expected that the level of circulating active ingredients in Ovestin Cream is increased.
- Women with pre-existing hypertriglyceridemia should be followed closely during estrogen replacement or hormone replacement therapy, since rare cases of large increases of plasma triglycerides leading to pancreatitis have been reported with estrogen therapy in this condition.
- There is no conclusive evidence for improvement of cognitive function. There is some evidence from WHI trial of increased risk of probable dementia in women who start using continuous combined CEE and MPA after the age of 65. It is unknown whether the findings apply to younger post-menopausal women or other HRT products.
- Ovestin cream contains cetyl alcohol and stearyl alcohol. This may cause local skin reactions (e.g. contact dermatitis).

4.5 Interactions with other medicinal products and other forms of interaction

No examples of interactions between Ovestin and other medicines have been reported in clinical practice. Although data are limited, interactions between Ovestin and other medicinal products may occur. The following interactions have been described with use of combined oral contraceptives which may also be relevant for Ovestin. The metabolism of estrogens may be increased by concomitant use of substances known to induce drug-metabolising enzymes, specifically cytochrome P450 enzymes, such as anticonvulsants (e.g. hydantoins, barbituates, carbamezapin), anti-infectives (e.g. griseofulvin, rifamycins, the antiretroviral agents nevirapine and efavirenz) and herbal preparations containing St John's wort (Hypericum Perforatum). Ritonavir and nelfinavir, although known as strong inhibitors, by contrast exhibit inducing properties when used concomitantly with steroid hormones.

Clinically, an increased metabolism of estrogens may lead to decreased effectiveness of Ovestin and changes in uterine bleeding profile.

Estriol may possibly increase the pharmacological effects of corticosteroids, succinylcholine, theophyllines and troleandomycin.

During clinical trials with the combination drug regimen ombitasvir hydrate/paritaprevir hydrate/ritonavir with or without dasabuvir, ALT elevations to greater than 5 times the upper limit of normal (ULN) were significantly more frequent in female subjects using ethinyl estradiol-containing medications. Women using estrogens other than ethinyl estradiol, such as estradiol, estriol and conjugated estrogens had a rate of ALT elevation similar to those not receiving any estrogens; however, due to the limited number of subjects taking these other estrogens, caution is warranted for co-administration with the combination drug regimen ombitasvir hydrate/paritaprevir hydrate/ritonavir with or without dasabuvir. (See section 4.4.)

4.6 Pregnancy and lactation

Ovestin is not indicated during pregnancy. If pregnancy occurs during medication with Ovestin, treatment should be withdrawn immediately. The results of most epidemiological studies to date relevant to inadvertent foetal exposure to estrogens indicate no teratogenic or foetotoxic effects.

Ovestin is not indicated during lactation.
Estriol is excreted in breast milk and may decrease milk production.

4.7 Effects on ability to drive and use machines

As far as is known Ovestin has no effect on alertness and concentration.

4.8 Undesirable effects

The following adverse reactions, associated with estrogen treatment may occur during estriol therapy or overdose: Nausea and vomiting, breast tenderness or pain in the breasts, vaginal bleeding or spotting during or on withdrawal of therapy, excessive production of cervical mucus, headache.

From Literature and safety surveillance monitoring, the following adverse reactions have been reported:

System organ class	Adverse reactions*
General disorders and administration site conditions	Application site irritation and pruritus Influenza-like illness
Reproductive system and breast disorders	Breast discomfort and pain

*MedDRA version9.1

These adverse reactions are usually transient, but may also be indicative of too high a dosage.

Breast cancer risk

- An up to 2-fold increased risk of having breast cancer diagnosed is reported in women taking combined estrogen-progestagen therapy for more than 5 years.
- Any increased risk in users of estrogen-only therapy is substantially lower than that seen in users of estrogen-progestagen combinations.
- The level of risk is dependent on the duration of use (see section 4.4).
- Results of the largest randomized placebo-controlled trial (WHI-study) and largest epidemiological study (MWS) are presented.

Million Women study– Estimated additional risk of breast cancer after 5 years' use

Age range (yrs)	Additional cases per 1000 never-users of HRT over a 5 year period*	Risk ratio #	Additional cases per 1000 HRT users over 5 years (95%CI)
Estrogen only HRT			
50-65	*9-12*	*1.2*	*1-2 (0-3)*
Combined estrogen-progestagen			
50-65	*9-12*	*1.7*	*6 (5-7)*
#Overall risk ratio. The risk ratio is not constant but will increase with increasing duration on use * *Taken from baseline incidence rates in developed countries.*			

US WHI studies - additional risk of breast cancer after 5 years' use

Age range (yrs)	Incidence per 1000 women in placebo arm over 5 years	Risk ratio & 95%CI	Additional cases per 1000 HRT users over 5 years (95%CI)
CEE estrogen-only			
50-79	*21*	*0.8 (0.7 – 1.0)*	*-4 (-6 – 0)**
CEE+MPA estrogen & progestagen‡			
50-79	14	*1.2 (1-1.5)*	*+4 (0 – 9)*

‡When the analysis was restricted to women who had not used HRT prior to the study there was no increased risk apparent during the first 5 years of treatment: after 5 years the risk was higher than in non-users. * WHI study in women with no uterus, which did not show an increase in risk of breast cancer

Ovarian cancer

Long-term use of estrogen-only and combined estrogen-progestagen HRT has been associated with a slightly increased risk of ovarian cancer. In the Million Women Study 5 years of HRT resulted in 1 extra case per 2500 users.

Risk of venous thromboembolism

HRT is associated with a 1.3-3-fold increased relative risk of developing venous thromboembolism (VTE), i.e. deep vein thrombosis or pulmonary embolism. The occurrence of such an event is more likely in the first year of using HT (see section 4.4). Results of the WHI studies are presented:

WHI Studies - Additional risk of VTE over 5 years' use

Age range (yrs)	Incidence per 1000 women in placebo arm over 5 years	Risk ratio & 95%CI	Additional cases per 1000 HRT users
Oral estrogen-only			
50-59	**7**	*1.2 (0.6 – 2.4)*	*1 (-3 – 10)*
Oral combined estrogen-progestagen			
50-59	**4**	*2.3 (1.2 – 4.3)*	*5 (1 – 13*)

** Study in women with no uterus*

Risk of coronary artery disease

The risk of coronary artery disease is slightly increased in users of combined estrogen-progestagen HRT over the age of 60 (see section 4.4).

Risk of ischaemic stroke

The use of estrogen-only and estrogen-progestagen therapy is associated with an up to 1.5 fold increased relative risk of ischaemic stroke. The risk of haemorrhagic stroke is not increased during use of HRT. This relative risk is

not dependent on age or on duration of use, but as the baseline risk is strongly age-dependent, the overall risk of stroke in women who use HRT will increase with age, see section 4.4.

WHI studies combined - Additional risk of ischaemic stroke* over 5 years' use

Age range (years)	Incidence per 1000 women in placebo arm over 5 years	Risk ratio and 95%CI	Additional cases per 1000 HRT users over 5 years
50-59	8	1.3 (1.1– 1.6)	3 (1-5)

**no differentiation was made between ischaemic and haemorrhagic stroke.*

Other adverse reactions have been reported in association with estrogen-only and estrogen/progestagen combined treatment:

- Estrogen-dependent neoplasms benign and malignant, e.g. endometrial cancer.
- Gall bladder disease.
- Skin and subcutaneous disorders: chloasma, erythema multiforme, erythema nodosum, vascular purpura.
- Probable dementia over the age of 65 (see section 4.4).

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form: http://sideeffects.health.gov.il
Additionally, you can also report to www.perrigo-pharma.co.il

4.9 Overdose

The acute toxicity of estriol in animals is very low. Symptoms that may occur in the case of an acute oral overdosage are nausea, vomiting, and possibly withdrawal bleeding in females.

No specific antidote is known. If necessary a symptomatic treatment should be instituted.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: natural and semisynthetic estrogens

ATC code: G03CA04

Estriol: The active ingredient, synthetic estriol, is chemically and biologically identical to human estriol. It substitutes for the loss of estrogen production in menopausal women, and alleviates atrophic vaginitis.

Ovestin Cream contains the synthetic hormone estriol. In the years just before and after the menopause (whether naturally or surgically induced) estriol can

be used in the treatment of urogenital symptoms and complaints related to estrogen deficiency. In cases of vaginal atrophy estriol induces normalisation of the vaginal epithelium and thus helps to restore the normal microflora and a physiological pH in the vagina. As a result it increases the resistance of the vaginal epithelial cells to infection and inflammation.

Estriol is relatively short-acting estrogen due to its short nuclear retention time in endometrial cells, its low affinity for plasma proteins and partly as a result of this, its rapid metabolic clearance. Endometrial proliferation is not expected when estriol is given in a single daily dose, since this requires sustained, occupancy of the nuclear estrogen receptor. As a consequence, undesired vaginal bleeding rarely occurs during treatment with estriol and an increased risk of endometrial carcinoma is unlikely.

Relief of urogenital symptoms was achieved during the first weeks of treatment.

5.2 Pharmacokinetic properties

After administration of Ovestin Cream, estriol is also absorbed from the vagina into the general circulation, shown by a sharp rise in plasma estriol, followed by a gradual decline.

After 3 weeks of administration of a single daily dose, a similar absorption pattern to that seen for a single application was observed.

Daily treatment with 0.5 mg of estriol (in 0.5 g of cream) leads to a sharp rise in unconjugated plasma estriol levels to 110 pg/ml at one hour from previously undetectable levels (<12 pg/ml). This was followed by a gradual decline during the next 5 hours to around 60 pg/ml.

On day 21 of treatment, mean baseline estriol levels of about 26 pg/ml rose to a mean peak value of 95 pg/ml at 1 hour. A decline similar to that seen on day 1 was observed during the next 5 hours.

Vaginal administration permits the absorption of the active (unconjugated, or free) form of estriol into the blood for transport to the target tissues, prior to its inactivation via conjugation by enterohepatic enzymes.

5.3 Preclinical safety data

No particulars

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Purified water, glycerol, stearyl alcohol, octyldodecanol, cetyl alcohol, polysorbate 60, cetyl palmitate, sorbitan stearate, lactic acid, chlorhexidine dihydrochloride, sodium hydroxide.

6.2 Incompatibilities

None stated.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials

6.4 Special precautions for storage

Store below 25°C. Do not freeze.
Use within 35 days since first opening.

6.5 Nature and contents of containers

Aluminum tube containing 15 g cream with a polyethylene screw cap. Each tube is packed in a cardboard box together with an applicator.

6.6 Special precautions for disposal

Any unused medicinal product, the applicator or waste material should be disposed of in accordance with local requirements.

7. Manufacturer:

Aspen Pharma Trading Ltd., Dublin, Ireland
3016 Lake Drive
Citywest Business Campus
Dublin 24
Ireland

8. License Number

06560. 21266

9. License Holder

Padagis Israel Agencies Ltd.
1 Rakefet St., Shoham.

10. Date of Revision of Text

Revised in December 2021 according to MOH guidelines.

13.12.2021