

## NEW ZEALAND DATA SHEET

### **ESTRADOT<sup>®</sup>** **(oestradiol)**

**25, 37.5\*, 50, 75\* & 100 mcg/24 hrs Transdermal Patches**

## **Description and Composition**

### **Pharmaceutical form**

Transdermal patch.

### **Active substance(s)**

Estradot is available in three sizes:

- 2.5 cm<sup>2</sup> patch containing 0.39 mg oestradiol (as hemihydrate) with a nominal *in vivo* release rate of 25 micrograms oestradiol per day.
- 5 cm<sup>2</sup> patch containing 0.78 mg oestradiol (as hemihydrate) with a nominal *in vivo* release rate of 50 micrograms oestradiol per day.
- 10 cm<sup>2</sup> patch containing 1.56 mg oestradiol (as hemihydrate) with a nominal *in vivo* release rate 100 micrograms oestradiol per day.

### **Excipients**

Adhesive matrix: acrylic adhesive, silicone adhesive, oleyl alcohol, dipropylene glycol and povidone.

Backing layer: ethylene vinyl acetate/polyethylene copolymer and vinylidene chloride/vinyl chloride copolymer.

Release liner: Fluoropolymer-coated polyester.

### **Indications**

The Estradot regimen is indicated for the following:

- Oestrogen replacement therapy for the treatment of the symptoms of natural or surgically induced menopause.
- Prevention of postmenopausal osteoporosis (see Dosage and Administration and Warnings and Precautions).

In women with an intact uterus, oestrogens should always be supplemented by administration of a progestogen.

## Dosage and Administration

### Dosage

#### Adults and elderly

Hormone replacement therapy (HRT) involving either oestrogen-only or oestrogen-progestogen combined therapy should only be continued as long as the benefits outweigh the risks for the individual.

Estradot should be applied every 3 to 4 days (i.e. twice weekly).

#### Climacteric symptoms

Treatment should be initiated with the lowest dose. Depending on the clinical response the dose should be adjusted to the woman's individual needs. If, after three months, there is an insufficient response in the form of alleviated symptoms, the dose should be increased. If symptoms of overdose arise (e.g. tender breasts) the dose must be decreased. Maintenance therapy must always be at the lowest effective dose.

#### Prevention of postmenopausal osteoporosis

Treatment should be initiated with the lowest dose. Dose adjustments can be made by using other strengths of Estradot. The lowest effective dose should be used for maintenance therapy.

#### General instructions

Estradot is administered as **continuous** therapy (uninterrupted application twice weekly). In women with an intact uterus, Estradot should be combined with a progestogen approved for addition to oestrogen treatment as follows:

The progestogen is added either for the last 12 to 14 days of every 4-week cycle (**continuous-sequential**) or every day without interruption (**continuous-combined**).

In women not currently taking oral oestrogens or in women switching from another oestradiol transdermal therapy, treatment with Estradot may be initiated at any convenient time. In women who are currently taking oral oestrogens, treatment with Estradot should be initiated one week after withdrawal of oral hormone replacement therapy, or sooner if menopausal symptoms reappear within one week.

#### Method of application

The adhesive side of Estradot should be placed on a clean, dry area of the abdomen. *Estradot should not be applied to the breasts.*

Estradot should be replaced twice weekly. The site of application must be rotated, with an interval of at least 1 week allowed between applications to a particular site. The area selected should not be oily, damaged, or irritated. The waistline should be avoided, since tight clothing may dislodge the patch. The patch should be applied immediately after opening the sachet and

removing the protective liner. The patch should be pressed firmly in place with the palm of the hand for about 10 seconds, making sure there is good contact, especially around the edges. In the event that a patch should fall off, the same patch may be reapplied. If necessary, a new patch may be applied. In either case, the original treatment schedule should be continued. If a woman has forgotten to apply a patch, she should apply a new patch as soon as possible. The subsequent patch should be applied according to the original treatment schedule. The interruption of treatment might increase the likelihood of recurrence of symptoms.

## Children

Estradot should not be used in children.

## Contraindications

Estradot should not be used by women with any of the following conditions:

- Known, past or suspected breast cancer,
- Known or suspected cancer of the endometrium or other oestrogen-dependent neoplasia,
- Undiagnosed abnormal vaginal bleeding,
- Severe hepatic disease,
- History of or current venous thromboembolism (VTE) (i.e.. deep vein thrombosis, pulmonary embolism),
- Known thrombophilic disorders or thrombophlebitis,
- History of or current arterial thromboembolic disease (e.g. coronary heart disease, stroke),
- Porphyria,
- Known hypersensitivity to oestrogens or to any of the excipients,
- Known or suspected pregnancy,
- Breastfeeding.

## Warnings and Precautions

### Warnings

For all therapeutic indications, the lowest effective dose should be used and consideration should be given to the shortest duration of use. Treatment should only be continued as long as the benefits outweigh the risks for the Individual.

The Medicines Adverse Reactions Committee advises that combined HRT should not be used for longer than 3 – 4 years.

### Osteoporosis

When initiating HRT for the prevention of osteoporosis, careful consideration should be given to the benefits versus the risks for the individual. Potential alternative therapies should be considered if the risks outweigh the benefits. Periodic re-evaluation for continuing treatment is recommended.

## Contact sensitisation

Contact sensitisation is known to occur with all topical applications. Although it is extremely rare, women who develop contact sensitisation to any of the components of the patch should be warned that a severe hypersensitivity reaction may occur with continuing exposure to the causative agent.

## Cardiovascular disease

HRT should not be used for the prevention of cardiovascular disease.

Large clinical trials (Women's Health Initiative and Heart and Oestrogen/Progestin Replacement study) evaluated the risk of cardiovascular events with the HRT products used in these studies.

The Women's Health Initiative (WHI) studies were randomised clinical trials conducted with either continuous combined oral conjugated equine oestrogens (CEE) and medroxyprogesterone acetate (MPA) for an average follow-up of 5.2 years, or with oral CEE for an average follow-up of 6.8 years. In the WHI continuous combined oral HRT trial, the absolute excess risk of coronary heart disease was 7 additional cases per 10,000 person-years (37 versus 30) in HRT-treated women and the relative risk was 1.29. In the WHI oestrogen-only HRT trial, the use of CEE alone did not affect coronary heart disease incidence in postmenopausal women [11].

In addition, both WHI studies showed an increased incidence of stroke. In the trial of continuous combined oral CEE and medroxyprogesterone acetate (MPA), the absolute excess risk was 8 additional cases per 10,000 person-years (29 versus 21) in HRT-treated women and the relative risk was 1.41. The absolute excess risk in the trial of oestrogen/CEE was 12 additional cases per 10,000 person-years (44 versus 32) in HRT-treated women and the relative risk was 1.39.

The Heart and Oestrogen/Progestin Replacement Study (HERS), a controlled clinical trial using CEE and MPA for secondary prevention in postmenopausal women with documented heart disease, showed an increased risk of cardiovascular events in the first year of use and no cardiovascular benefit thereafter.

There have been no randomised controlled trials to date to assess the risk of cardiovascular morbidity or mortality, or stroke, with combined transdermal oestrogen-progestogen HRT products. Therefore there are no data to support the conclusion that the frequency of cardiovascular events and stroke is different with Estradot.

## Venous thromboembolism

Oestrogen-only and combined oestrogen-progestogen HRT are associated with a higher risk of developing venous thromboembolism (VTE), i.e. deep vein thrombosis or pulmonary embolism.

Some randomised controlled trials (e.g. WHI oestrogen-alone, WHI combined HRT and HERS), and epidemiological studies have found a two- to three-fold higher risk for users compared with non-users.

The WHI continuous combined study (see subsection Cardiovascular disease) showed an increased incidence of pulmonary embolism. The absolute excess risk was 8 additional cases per 10,000 person-years (15 versus 7) in HRT-treated women and the relative risk was 2.13.

The increase in risk was found only in current users and did not persist in former users. The risk appeared to be higher in the first years of use compared to later years.

For non-users, it is estimated that the number of cases of VTE that would occur over a 5-year period is about 3 per 1000 women aged 50 to 59 years and 8 per 1000 women aged 60 to 69 years. It is estimated that in healthy women who use HRT for 5 years, the number of additional cases of VTE would be between 2 and 6 per 1000 women aged 50 to 59 years and between 5 and 15 per 1000 women aged 60 to 69 years.

Risk/benefit should therefore be carefully weighed in consultation with the individual when prescribing HRT to women with a risk factor for the occurrence of VTE that is not already mentioned under 5 Contraindications.

Generally recognised risk factors for VTE include a personal history or family history of thromboembolic disease (the occurrence of VTE in a direct relative at a relatively early age may indicate genetic predisposition) obesity (Body Mass Index  $> 30 \text{ kg/m}^2$ ) and systemic lupus erythematosus (SLE). The risk of VTE also increases with age. There is no consensus about the possible role of varicose veins in VTE.

A history of recurrent spontaneous abortions should be investigated to exclude thrombophilic predisposition. In women in whom this diagnosis is confirmed, the use of HRT is viewed as contraindicated.

The risk of VTE may be temporarily increased by prolonged immobilisation, major elective or posttraumatic surgery, or major trauma. In women on HRT, scrupulous attention should be given to prophylactic measures to prevent VTE following surgery. Depending on the nature of the event and the duration of immobilisation, consideration should be given to temporarily stopping HRT several weeks earlier, if possible. Treatment should not be restarted until the woman is completely mobile.

Women should be told to contact their doctor immediately if they become aware of a potential thromboembolic symptom (e.g. painful swelling of a leg, sudden pain in the chest, dyspnoea). If venous thromboembolism develops after initiating therapy with Estradot, treatment should be immediately discontinued.

## **Breast cancer**

Randomised controlled trials and epidemiological studies have reported an increased risk of breast cancer in women taking HRT. Women using combined oestrogen-progestogen HRT had a possibly higher risk than women who used unopposed oestrogens. The excess risk of breast cancer increases with the duration of intake of combined oestrogen-only and combined oestrogen-progestogen HRT.

There is evidence arising from the WHI continuous combined study (see subsection Cardiovascular disease) which shows an absolute excess risk of invasive breast cancer of 8 additional cases per 10,000 person-years (38 versus 30) in the HRT-treated women and a relative risk of 1.26.

In a meta-analysis of 51 epidemiological studies conducted between the 1970s and the early 1990s, the cumulative incidence of breast cancer in non-users of HRT between the ages of 50 and 70 is about 45 per 1000 women. The cumulative excess numbers of cases of breast cancer diagnosed per 1000 women who began use of HRT between the ages of 50 and 70, and used it for 5, 10 or 15 years, is estimated to be 2, 6, and 12, respectively.

The number of additional cases of breast cancer is broadly similar among women who start HRT between the ages of 45 and 65 regardless of their age at the start of treatment.

The excess risk seems to return to baseline in the course of about five years following cessation of treatment.

For transdermal oestrogen-only and oestrogen-progestogen combined HRT products, no large randomised clinical trials to date have assessed the HRT-associated risk of breast cancer. Therefore there are no data to support the conclusion that the frequency of breast cancer is different with Estradot.

Women should be advised that 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 and adapted to the clinical needs of the individual woman.

Unopposed oestrogen stimulation may lead to premalignant or malignant transformation in the residual foci of endometriosis. Therefore, the addition of a progestogen to oestrogen replacement therapy is recommended in women who have undergone hysterectomy and who are known to have residual endometriosis.

## **Endometrial cancer**

The risk of endometrial cancer in users of unopposed oestrogens who have an intact uterus is greater than in non-users and appears to depend on the duration of treatment and the oestrogen dose. The greatest risk appears to be associated with prolonged use. It has been shown that adequate concomitant progestogen therapy lowers the incidence of endometrial hyperplasia and therefore the potential risk of endometrial carcinoma associated with prolonged use of oestrogen therapy.

Oestrogens, regardless of their origin, increase the risk of endometrial cancer. Close clinical surveillance of all women taking oestrogens is important. Adequate diagnostic measures, including endometrial sampling when indicated, should be undertaken to rule out malignancy in all cases of undiagnosed persistent or recurring abnormal vaginal bleeding.

In all cases of undiagnosed persistent vaginal bleeding or spotting, adequate diagnostic measures, including endometrial sampling when indicated, should be undertaken to rule out abnormality and treatment should be re-evaluated.

## **Ovarian cancer**

An increased risk of ovarian cancer in menopausal women taking oestrogen only replacement therapy was observed in a large US study enrolling over 40,000 women on HRT. These women were followed up for a mean duration of 13.4 years (range 1 month to 19.8 years). The increased risk of ovarian cancer in those taking oestrogen replacement therapy was 80%, RR 1.8 (95% CI, 1.1-3.0) at 10 to 19 years. This risk increased with duration of use; RR for 20 years or more years of use was 3.2 (95% CI, 1.7 -5.7). This equates to approximately 3 and 8 additional cases per 10,000 women-years at these time points; (the incidence of ovarian cancer in non-users was 4.4 per 10,000 women years). This observation was most obvious in those women on long-term oestrogen replacement therapy who had a prior history of hysterectomy (defined as simple hysterectomy or hysterectomy with unilateral oophorectomy). In this subpopulation, the RR was 2.0 (95%CI, 0.96-4.3) for between 10 and 19 years of use and 3.4 (95% CI, 1.6-7.5) for 20 years or more.

## Dementia

In a randomised placebo-controlled ancillary study of the WHI, the Women's Health Initiative Memory Study (WHIMS), women aged 65 and older (average age 71) treated with oral CEE and MPA for an average follow-up of 4 years were reported to have a two-fold increase in the risk of developing probable dementia. The absolute excess risk of probable dementia was 23 additional cases per 10,000 person-years (45 versus 22) in CEE/MPA treated women and the relative risk was 2.05.

In a randomised, placebo-controlled, oestrogen alone ancillary study of the WHI (WHIMS), the absolute excess risk of probable dementia after an average follow-up of 5.2 years was 12 additional cases per 10,000 person-years (37 versus 25) in CEE treated women and the relative risk was 1.49, which did not reach statistical significance ( $p = 0.18$ ) compared to placebo.

Since both sub-studies were conducted in women aged 65 to 79 years, it is unknown whether these findings apply to younger postmenopausal women.

For transdermal oestrogen-only or oestrogen-progestogen combined products, no large randomised clinical trials have assessed the HRT-associated risk of probable dementia to date. Therefore there are no data to support the conclusion that the frequency of probable dementia is different with Estradot.

## Angioedema

Oestrogens may induce or exacerbate symptoms of angioedema, in particular in women with hereditary angioedema

## Precautions prior to initiation of Estradot therapy

Before initiating or re-instituting HRT, a complete personal and family medical history, and an appropriate physical (including pelvic and breast) examination should be performed (see Contraindications and Warnings and Precautions).

Consideration should be given to the lowest dose and the shortest duration of use.

Hysterectomized women who require postmenopausal hormone replacement therapy should receive oestrogen-only replacement therapy unless otherwise indicated (e.g. endometriosis).

Caution is advised when risk factors for oestrogen-dependent tumours (e.g. first-degree blood relatives who have ever had breast cancer) are present.

Women should be advised that Estradot is not a contraceptive nor will it restore fertility.

## Monitoring during Estradot therapy

During treatment, periodic check-ups of a nature and frequency adapted to the individual woman are recommended. A careful appraisal of the risks and benefits should be undertaken over time in women treated with HRT and the need for HRT should be re-evaluated periodically.

If any of the following conditions are present or have occurred previously (including during pregnancy or a previous hormone treatment), the woman should be closely monitored, in particular: leiomyoma (uterine fibroids) or endometriosis, thromboembolic disorders, heart failure, hypertension, hepatic disorders (e.g. liver adenoma), renal disorders, diabetes mellitus

with or without vascular involvement, cholelithiasis, migraine or severe headache, systemic lupus erythematosus, endometrial hyperplasia, epilepsy, asthma, otosclerosis, gallbladder disease, oestrogen-related jaundice and pruritus.

It should be taken into account that these conditions may recur or be aggravated during treatment with oestrogens.

If worsening of any of the above mentioned conditions is diagnosed or suspected during HRT, the benefits and risks of HRT should be reassessed on an individual basis.

Oestrogens may cause fluid retention and therefore women with cardiac or renal dysfunction should be carefully monitored.

Women with hypertriglyceridaemia should be followed closely during HRT, since rare cases of large increases of plasma triglycerides leading to pancreatitis have been reported with oral oestrogen therapy in these women.

Although observations to date suggest that oestrogens, including transdermal oestradiol, do not impair carbohydrate metabolism, diabetic women should be monitored during initiation of therapy until further information is available.

Thyroid function should be monitored regularly in patients who require thyroid hormone replacement therapy and who are also taking oestrogen in order to ensure that thyroid hormone levels remain within an acceptable range

### **Discontinuation of Estradot therapy**

Therapy should be discontinued in the following situations: jaundice or deterioration of liver function, a significant increase in blood pressure, new onset of migraine-type headache and pregnancy, or if a condition described under Contraindications develops.

When Estradot therapy is combined with cyclic progestogen administration, there are often occurrences of breakthrough bleeding and spotting during the initial months of treatment.

In all cases of undiagnosed persistent or irregular vaginal bleeding, adequate diagnostic measures, including endometrial sampling when indicated, should be undertaken to rule out abnormality and the treatment should be re-evaluated.

### **Interactions**

Metabolism of oestrogens and progestogens may be increased by concomitant use of substances known to induce drug-metabolising enzymes, specifically cytochrome P450 enzymes, such as anticonvulsants (e.g. carbamazepine, phenytoin, phenobarbital), meprobamate, phenylbutazone and anti-infectives (e.g. rifampicin, rifabutin, nevirapine, efavirenz).

Caution should be used if the woman is receiving protease inhibitors (e.g. ritonavir and nelfinavir), which are known as strong inhibitors of cytochrome P450 enzymes, and by contrast exhibit inducing properties when used concomitantly with steroid hormones.

Herbal preparations containing St. John's wort (*Hypericum perforatum*) may induce the metabolism of oestrogens and progestogens.

Clinically, increased metabolism of oestrogens and progestogens may lead to decreased effects and changes in the uterine bleeding profile.

With transdermal HRT administration, the first-pass effect in the liver is avoided and thus transdermally applied oestrogens may be less affected by enzyme inducers than oral hormones.

Some laboratory tests may be influenced by oestrogen therapy, such as tests for glucose tolerance or thyroid function.

## Pregnancy and Breastfeeding

### Pregnancy

Estradot must not be used during pregnancy. Both oestrogens and progestogens may cause foetal harm when administered to a pregnant woman.

### Breastfeeding

Estradot must not be used while breastfeeding.

### Driving and using machines

No known effects.

### Adverse drug reactions

Adverse drug reactions from clinical trials (Table 1) and post-marketing experience are listed according to the system organ class in MedDRA. Within each system organ class, the adverse drug reactions are ranked by frequency, the most frequent first. Within each frequency grouping, adverse drug reactions are presented in the order of decreasing seriousness. In addition the corresponding frequency using the following convention (CIOMS III) is also provided for each adverse drug reaction: very common ( $\geq 1/10$ ); common ( $\geq 1/100, < 1/10$ ); uncommon ( $\geq 1/1,000, < 1/100$ ); rare ( $\geq 1/10,000, < 1/1,000$ ); very rare ( $< 1/10,000$ ), including isolated reports and not known.

**Table 1**

<b>Neoplasms benign, malignant and unspecified (including cysts and polyps)</b>	
Uncommon:	Breast cancer.
<b>Immune system disorders</b>	
Not known <sup>(1)</sup> :	Hypersensitivity.
<b>Psychiatric disorders</b>	
Common:	Depression.
Not known <sup>(1)</sup> :	Nervousness, affect liability
<b>Nervous system disorders</b>	
Common:	Headache, Migraine, dizziness.
<b>Cardiac disorders</b>	
Not known	Embolism, hypertension
<b>Gastrointestinal disorders</b>	
Common:	Nausea, abdominal pain, abdominal distension.
Uncommon:	Vomiting.
Not known <sup>(1)</sup> :	Cholelithiasis, liver function tests abnormal, diarrhoea
<b>Skin and subcutaneous tissue disorders</b>	
Uncommon:	Alopecia, hirsutism.
Not known <sup>(1)</sup> :	Erythema nodosum, erythema multiforme, rash generalised, pruritus

	generalised
<b>Musculoskeletal and connective tissue disorder</b>	
Not known	Back pain, pain in extremity
<b>Reproductive system and breast disorders</b>	
Very common:	Breast tenderness.
Common:	Menstrual disorders (changes in vaginal bleeding pattern and abnormal withdrawal bleeding or flow), metrorrhagia, cervical discharge, breast enlargement.
Uncommon:	Genital candidiasis, uterine leiomyoma.
Not known <sup>(1)</sup> :	Endometrial hyperplasia, breast discomfort, breast pain
<b>General disorders and administration site conditions</b>	
Very common:	Application site reaction (at the patch application site, observed after removing the patch by peeling from the skin).
Common:	Weight fluctuation, oedema, pruritus and rash (around the application site).
Uncommon:	Libido increased or decreased.

<sup>(1)</sup> Reported in post-marketing experience.

Other adverse reactions have been reported in association with some oestrogen-progestogen treatments:

- Oestrogen-dependent neoplasms, benign and malignant, e.g. endometrial cancer,
- Embolism venous, e.g. deep leg or pelvic venous thrombosis and pulmonary embolism,
- Cerebrovascular accident,
- Myocardial infarction,
- Cholestatic jaundice,
- Gallbladder disease,
- Aggravation of porphyria,
- Dementia
- Chorea,
- Contact lens intolerance (dry eyes and tear film compositions changes),
- Purpura,
- Chloasma,
- Carbohydrate tolerance decreased.

## Overdosage

Acute overdosage is unlikely due to the mode of administration. The most common symptoms of overdosage in clinical use are breast tenderness and/or vaginal bleeding. If such symptoms occur, a reduction in dosage should be considered. The effects of overdosage can be rapidly reversed by removal of the patch.

## Clinical Pharmacology

### Pharmacodynamic properties (PD)

Pharmacotherapeutic group: Oestrogens (ATC code G03CA03)

The active substance in Estradot, 17beta-oestradiol, is chemically and biologically identical to the endogenous human 17beta-oestradiol and is classified as a natural oestrogen. It compensates for the decreasing oestrogen production in menopausal women and alleviates

menopausal symptoms. Oestradiol prevents bone loss after the menopause or after an ovariectomy.

### **Pharmacokinetic properties (PK)**

Transdermal administration of oestradiol achieves therapeutic plasma concentrations using a lower total dose of oestradiol than required with oral administration. Plasma levels of estrone and estrone conjugates are also lower with the transdermal route.

Oestradiol is more than 50% bound to plasma proteins such as sex-hormone-binding globulin and albumin. The sulfate and glucuronide esters along with a small proportion of oestradiol and several other metabolites are excreted in the urine. Only a small amount is excreted in faeces.

In studies in postmenopausal women with application of 2.5, 3.75, 5 and 10 cm<sup>2</sup> Estradot patches, average peak oestradiol serum levels ( $C_{max}$ ) were approximately 25 pg/mL, 35 pg/mL, 50-55 pg/mL and 95-105 pg/mL, respectively. Linear pharmacokinetics have been demonstrated for oestradiol following transdermal administration.

Since oestradiol has a short half-life (approximately one hour), serum concentrations of oestradiol and estrone returned to baseline values within 24 hours following removal of the patch.

At steady state, after repeated applications of 5 cm<sup>2</sup> (50 micrograms/day) Estradot patches, oestradiol  $C_{max}$  and  $C_{min}$  values (57 and 28 pg/mL, respectively) were similar to those in the single application study, while estrone  $C_{max}$  and  $C_{min}$  values were lower (42 and 31 pg/mL, respectively).

### **Non-clinical safety data**

The toxicity profile of oestradiol has been well established. Long-term continuous administration of natural and synthetic oestrogens in certain animal species increases the frequency of carcinomas of the breast, uterus, cervix, vagina, testis, and liver.

## **Pharmaceutical information**

### **Incompatibilities**

No incompatibilities with other medicaments are known.

### **Special precautions for storage**

Store at or below 25°C. Do not refrigerate or freeze.

The patches should not be stored once opened but should be applied immediately upon removal from the protective sachet.

Estradot patches must be kept out of the reach and sight of children.

### **Nature and contents of container**

Packs contain 8 patches. Each Estradot patch is individually sealed in an aluminium laminate sachet.

\* These presentations are not available in New Zealand

**Instructions for and handling**

See “Dosage and Administration”.

After use, Estradot patch should be folded (adhesive surfaces pressed together) and discarded in such a way as to keep them out of the reach and sight of children.

**Medicine classification**

Prescription Medicine

**Name and address**

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