HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

Opinion
28 May 2014

DIVINA tablet
B/1 blister of 10 blue tablets and 11 white tablets (CIP: 3400933443559)
DUOVA 1 mg/2.5 mg, tablet
B/1 blister of 28 tablets (CIP: 3400935784902)
DUOVA 1 mg/5 mg, tablet
B/1 blister of 28 tablets (CIP: 3400935785152)
DUOVA 2 mg/5 mg, tablet
B/1 blister of 28 tablets (CIP: 3400935785381)

Applicant: CENTRE SPECIALITÉS PHARMACEUTIQUES

INN	DIVINA tablet: Blue tablet: estradiol valerate / medroxyprogesterone acetate White tablet: estradiol valerate DUOVA 1 mg/2.5 mg, DUOVA 1 mg/5 mg, DUOVA 2 mg/5 mg, tablet estradiol valerate / medroxyprogesterone acetate
ATC code (2013)	DIVINA tablet: G03FB06 (progestogens and oestrogens, sequential preparations) DUOVA 1 mg/2.5 mg, DUOVA 1 mg/5 mg, DUOVA 2 mg/5 mg, tablet: G03FA12 (progestogens and oestrogens, fixed combinations)
Reason for the review	**Reassessment of the Actual Benefit of all medicines indicated in hormone replacement therapy for menopause at the request of the Committee, pursuant to Article R-163-21 of the French Social Security Code** **Renewal of inclusion**
Lists concerned	**National Health Insurance** (French Social Security Code L.162-17) **Hospital use** (French Public Health Code L.5123-2)
Indications concerned	**DIVINA tablet:** **"-Hormone replacement therapy (HRT) for oestrogen deficiency symptoms in menopausal women.** **- Prevention of osteoporosis in postmenopausal women at high risk of future fractures who are intolerant of or contraindicated for other medicinal products approved for the prevention of osteoporosis.** **Experience of treating women older than 65 years is limited. "** **DUOVA 1 mg/2.5 mg, DUOVA 1 mg/5 mg, DUOVA 2 mg/5 mg, tablet:** **"- Hormone Replacement Therapy (HRT) for oestrogen deficiency symptoms in non-hysterectomised postmenopausal women with more than three years**

	postmenopause. **- Prevention of osteoporosis in postmenopausal women at high risk of future fractures who are intolerant of or contraindicated for other medicinal products approved for the prevention of osteoporosis.** **Experience of treating women older than 65 years is limited. "**

01 ADMINISTRATIVE AND REGULATORY INFORMATION

Marketing Authorisation	DIVINA: 02 December 1991 (national procedure) DUOVA: 1 mg/2.5 mg, 1 mg/5 mg, 2 mg/5 mg: 15 November 2001 (mutual recognition procedure)
Prescribing and dispensing conditions	List I

02 TRANSPARENCY COMMITTEE CONCLUSIONS

According to the evaluation report attached to this opinion, the Committee believes that:

02.1 ACTUAL BENEFIT

2.1.1 Hormone replacement therapy (HRT) for oestrogen deficiency symptoms in menopausal women.

◗ Vasomotor symptoms of menopause when they are frequent and intense may significantly impair quality of life.

◗ These proprietary medicinal products are intended as symptomatic therapy.

◗ The efficacy/adverse effects ratio is moderate in patients with climacteric disorders that are described as troublesome enough to impair their quality of life and in compliance with the Committee's recommendations.

◗ There are treatment alternatives to these proprietary medicinal products (other hormonal treatments for menopause).

◗ Menopausal hormonal therapies are first-line therapies for climacteric disorders when they are troublesome enough to impair quality of life.

◗ Public health benefit

At the time of menopause, in the general population, the proportion of women complaining of climacteric disorders is supposedly more than 50%.[1] The most common symptom is hot flashes; approximately one in three women present with night sweats. However, there may be other symptoms: vaginal dryness or urinary symptoms. The frequency and severity of these symptoms decrease with time but are still present 10 years after menopause in approximately one out of four women.

As a result, given the limitations of their use in menopausal women, HRTs have little impact on public health.

Consequently, the Committee considers that the actual benefit of the proprietary medicinal products DIVINA and DUOVA 1 mg/2.5 mg, 1 mg/5 mg, 2 mg/5 mg in hormone replacement therapy (HRT) for symptoms of oestrogen deficiency in menopausal women remains substantial in patients for whom climacteric disorders are described as troublesome enough to impair their quality of life when these proprietary medicinal products are used as per the Committee's recommendations.

[1] ANAES [National Health Accreditation and Assessment Agency]/ANSM [French National Agency for Medicines and Health Products Safety] Traitements hormonaux substitutifs de la ménopause. Rapport d'orientation, 11 May 2004

2.1.2 Prevention of osteoporosis in postmenopausal women at high risk of future fractures who are intolerant of, or contraindicated for, other medicinal products approved for the prevention of osteoporosis.

◗ Postmenopausal osteoporosis is a serious disorder because of the risk of fractures. Femoral neck fractures in particular may be life-threatening.

◗ The proprietary medicinal product is intended as preventive therapy.

◗ Only for the duration of treatment, the efficacy/adverse effects ratio is high in the event of climacteric disorders and recent menopause, after a minor fracture or if there is a low T-score, in the case of intolerance to or failure of other treatments indicated in the prevention of osteoporosis.

◗ There are treatment alternatives (other hormonal treatments for menopause with the same indication).

◗ This proprietary medicinal product is intended as backup therapy.

◗ Public health benefit

Because of its high prevalence and the severity of its consequences, the public health burden of postmenopausal osteoporosis is substantial.

Given the role of hormonal menopause treatments in the management of osteoporosis, the number of patients for whom hormonal menopause treatments are indicated is very low.

Consequently, HRT does not have an impact on public health in this indication.

Consequently, the Committee considers that the actual benefit of the proprietary medicinal products remains substantial in the prevention of postmenopausal osteoporosis in women at increased risk of osteoporotic fracture and who are intolerant to or contraindicated for the other treatments indicated for the prevention of osteoporosis in the event of climacteric disorders and recent menopause, after a minor fracture or if there is a low T-score, when this proprietary medicinal product is used as per the Committee's recommendations.

03 TRANSPARENCY COMMITTEE RECOMMENDATIONS

The Committee recommends:

- Carefully weighing the benefit of hormone therapy against the symptoms and their impact on the patient's quality of life.
- Prescribing these treatments in accordance with their contraindications, in particular concerning the risk of thromboembolism and breast cancer.

These treatments should be prescribed when the climacteric disorders are described by the patient as troublesome enough to impair their quality of life, at the lowest effective dose, for the shortest duration possible as per the AFSSAPS's guidelines (see the appendix), in particular:

- before initiating or reinstituting HRT, a complete clinical and gynaecological examination (including an analysis of the family history) should be performed. A regular breast examination should be performed as per the current recommendations (palpation, mammography, ultrasound, etc.) and tailored to individual cases.
- at the start of treatment, patients must be given all relevant information enabling an appropriate and informed prescription. Thus, patients must be informed of the risks inherent to the treatment. In addition, the treatment should be re-assessed regularly, at least once a year, taking into account changes in the benefit/risk ratio. The treatment may be temporarily suspended during this reassessment in order to verify the persistence of the climacteric syndrome and its severity.

In the prevention of postmenopausal osteoporosis in women at increased risk of osteoporotic fracture and who are intolerant to, or contraindicated for, the other treatments indicated for the prevention of osteoporosis, these treatments should be prescribed in the event of climacteric disorders and recent menopause, after a minor fracture or if there is a low T-score.

The Committee recommends continued inclusion on the list of medicines refundable by National Health Insurance and on the list of medicines approved for hospital use in the indications in the Marketing Authorisation and as recommended by the Committee.

◗ **Proposed reimbursement rate: 65%**