



HAUTE AUTORITÉ DE SANTÉ

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TRANSPARENCY COMMITTEE

OPINION

18 July 2007

ENANTONE SR 3.75 mg, sustained-release powder and solvent for suspension for injection (SC or IM) (CIP: 375 752-5)

ENANTONE SR 11.25 mg, sustained-release microspheres and solution for injection (SC or IM) (CIP: 375 753-1)

Applicant: TAKEDA

Leuprorelin

ATC code: L02AE02

Date of Marketing Authorisation (MA): 25 June 1998 (11.25 mg dosage) and 16 August 1988 (3.75 mg dosage) ; MA modification of 28 September 2006

Reason for request: inclusion on the list of medicines reimbursed by National Insurance and approved for use by hospitals in the extension of indication “treatment of **locally advanced** prostate cancer”:

1 CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient

Leuprorelin

1.2. Indications

For the 11.25 mg dosage:

- Treatment of **locally advanced** or metastatic prostate cancer.
- Treatment of endometriosis at genital and extragenital localisations (from stage I to stage IV)
 - Clinical experience concerning the treatment of endometriosis is restricted to women aged 18 years or more.
 - Duration of treatment: cf. SPC
- Treatment of confirmed central precocious puberty (before 8 years in girls, before 10 years in boys).

For the 3.75 mg dosage:

- Treatment of **locally advanced** or metastatic prostate cancer.
- Treatment of confirmed central precocious puberty (before 8 years in girls, before 10 years in boys).
- Treatment of endometriosis at genital and extragenital localisations (from stage I to stage IV).
 - Clinical experience concerning the treatment of endometriosis is restricted to women aged 18 years or more.
 - Duration of treatment: cf. SPC
- Treatment of hormone-dependant metastatic breast cancer in premenopausal woman when suppression of ovarian function is necessary.
- Preoperative treatment of uterine fibroids:
 - associated with anaemia (haemoglobin concentration of not more than 8 g/dl),
 - or when a reduction in the size of the fibroid is required to facilitate or modify the surgical method: endoscopic surgery, transvaginal surgery.The duration of treatment is limited to 3 months.

1.3. Dosage

Treatment of locally advanced or metastatic prostate cancer:

One subcutaneous injection to be repeated every four weeks (3.75 mg dosage).

One subcutaneous or intramuscular injection to be repeated every 3 months (11.25 mg dosage).

2 SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification (2005)

L	: Antineoplastic and immunomodulator products
L02	: Endocrine therapy
L02A	: Hormones and related compounds
L02AE	: Hormone analogues inducing the release of gonadotrophins
L02AE02	: Leuprorelin

2.2. Medicines in the same therapeutic category

Comparator medicines

These are GnRH analogs indicated in the treatment of advanced prostate cancer:

Goserelin:

- ZOLADEX 10.8 mg, implant in prefilled syringe for subcutaneous injection
- ZOLADEX 3.6 mg, implant in prefilled syringe for subcutaneous injection

Indicated as adjuvant treatment to external radiotherapy in locally advanced prostate cancer (stage T3 - T4 of TNM classification or stage C of AUA classification).

Leuprorelin:

- ELIGARD 22.5 mg, powder and solvent for solution for injection
- ELIGARD 7.5 mg, powder and solvent for solution for injection

Indicated in the treatment of advanced hormone-dependant prostate cancer.

Triptorelin:

- GONAPEPTYL 3.75 mg, sustained-release powder and solvent for suspension for injection in pre-filled syringes

Indicated in the treatment of advanced hormone-dependant prostate cancer.

- DECAPEPTYL L.P. 11.25 mg, Powder and solvent for suspension for injection (IM), 3-month sustained-release formulation

- DECAPEPTYL L.P. 3 mg, Powder and solvent for suspension for injection (IM), 28-day sustained-release formulation

Indicated in the treatment of locally advanced or metastatic prostate cancer.

2.3. Medicines with a similar therapeutic aim

Anti-androgens and cytotoxic drugs indicated in the treatment of advanced prostate cancer.

3 ANALYSIS OF AVAILABLE DATA

The dossier comprises 2 studies:

- A randomised, open-label study *versus* triptorelin (Abou, 1997) evaluating the reduction in serum testosterone concentrations in patients with metastatic prostate cancer. This study enrolled patients only at the metastatic stage which is an indication not evaluated here (locally advanced stage). It is therefore not discussed in this document.
- Comparative study of two sustained-release Enantone formulations: 3.75 mg administered monthly and 11.25 mg administered every three months in patients with locally advanced or metastatic prostate cancer.

3.1. Efficacy

Randomised (2:1 ratio), open-label, phase II study¹ evaluating the efficacy and safety of two dosage of Enantone SR, 3.75 mg administered subcutaneously once monthly and 11.25 mg administered subcutaneously every three months, in 237 patients with locally advanced or metastatic prostate cancer. The total duration of treatment was nine months.

The primary endpoint was the reduction in testosterone concentrations during the treatment period.

Secondary endpoints: PSA levels, tumour response and safety.

Results:

The locally advanced stage accounted for 43% of cases.

After one month of treatment, the mean serum testosterone concentrations were lower than castration levels (< 50 ng/dL) and these were maintained throughout the treatment period.

At 9 months, PSA concentrations were lower than or equal to 4 ng/ml (threshold of normal PSA levels = 4 ng/ml) in 65% of the patients in the group treated every month and 66% in patients treated every three months.

A complete tumour response was observed in 4 patients in the group treated every month and in 9 patients treated every three months.

3.2. Adverse effects

The main adverse effects noted during treatment by the two forms of Enantone were signs of androgen deficiency, in particular impotence and hot flushes.

¹ Wechsel HW, Zerbib M, Pagano F, Coptcoat MJ. Randomized open labelled comparative study of the efficacy, safety and tolerability of leuprorelin acetate 1M and 3M depot in patients with advanced prostatic cancer. Eur Urol. 1996;30 Suppl 1:7-14; discussion 19-21

3.3. Conclusion

The efficacy and safety of Enantone were evaluated in a randomised, open-label, phase II study enrolling 237 patients with locally advanced or metastatic prostate cancer. Two dosage of Enantone SR were compared: 3.75 mg administered subcutaneously once a month and 11.25 mg administered subcutaneously every three months. The total duration of treatment was nine months.

After one month of treatment, the mean serum testosterone concentrations were lower than castration levels (< 50 ng/dL) and these levels were maintained throughout the treatment period.

At 9 months, PSA concentrations were lower than or equal to 4 ng/ml (threshold of normal PSA levels = 4 ng/ml) in 65% of the patients in the group treated monthly and 66% in patients treated every three months.

The main adverse events recorded during treatment by the two formulations of Enantone were signs of androgen deficiency with, in particular, impotence and hot flushes.

No study has been carried out to compare leuprorelin (ENANTONE) with another GnRH agonist in the management of these patients.

4 TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit

Prostate cancer is life-threatening;
These proprietary products are intended as curative treatment;
The efficacy/adverse effects ratio is high;
These proprietary products are intended for first line treatment;
There are other alternative medications.

Expected Public Health Benefit:

Prostate cancer is a frequent and serious clinical condition which represents a considerable public health burden. The burden induced by non-metastatic, locally advanced stages is moderate because of the smaller number of patients concerned.

Improving treatment of prostate cancer is a public health need. However, the proprietary product ENANTONE does not provide a different response to this need than other analogues used in the same indication.

A review of the clinical trial data and results obtained with other existing therapies shows that the proprietary product ENANTONE is not expected to have a benefit in terms of morbidity and mortality.

Consequently the proprietary product ENANTONE is not expected to benefit public health.

The actual benefit of ENANTONE is substantial.

4.2. Improvement in actual benefit

ENANTONE SR 3.75 mg and 11.25 mg, do not improve actual benefit (level V) compared to other GnRH analogues in the treatment of locally advanced prostate cancer.

4.3. Therapeutic use

According to the Recommendations of the French Urology Society (2004):

“At the locally advanced stage

The different treatment options in locally advanced prostate cancer are mainly:

- Treatment combining radiotherapy and hormone therapy
- Monitoring with delayed hormone treatment
- Total prostatectomy alone or combined with an adjuvant treatment (radiotherapy, hormone therapy)
- Hormone therapy.

Stage T3:

- Combination hormone therapy-radiotherapy is currently the reference treatment for locally advanced (T3) tumours in patients with a life expectancy of more than 10 years. Neo-adjuvant hormone therapy reduces tumour volume and may relieve the side effects of radiation. Hormone therapy may potentiate the effect of radiotherapy and improves the results in terms of local control and clinical and biochemical relapse-free survival.
- An abstention-monitoring approach may be proposed in elderly patients with a life expectancy less than or equal to 5 or 10 years, with asymptomatic or slow-growing disease or refusing the side effects of treatment. Hormone therapy is proposed during progression. Regular monitoring is necessary.
- Total prostatectomy may be proposed for a well-circumscribed, low grade T3 tumour with PSA<20 ng/ml, or with microscopic single-node involvement during the extemporaneous

investigation by lymph node dissection when the life expectancy is greater than 10 years. Neo-adjuvant hormone therapy before total prostatectomy is not recommended.

- Initially reserved for metastatic prostate cancer, the immediate use of hormone therapy alone in locally advanced forms is now backed by a professional consensus for high-growing tumours. A few publications have shown that immediate hormone therapy is associated with a better survival than deferred treatment in locally advanced disease.

Stage T4:

The group of T4 patients is a very mixed group in which a few patients initially have a prognosis of loco-regional progression. Hormone therapy is the reference treatment in T4 Nx*. There is no evidence suggesting that combined treatment by hormone therapy and external radiotherapy produces better results than hormone therapy alone. The primary objective of treatment is to improve quality of life.”

* Lymph node status not evaluated

4.4. Target population

The target population of ENANTONE within the scope of this extension of indication comprises patients with locally advanced prostate cancer (T3 and T4).

In France, the incidence of prostate cancer was estimated to be approximately 40,000 cases in 2000².

According to the data derived from a sample of 5 of the 8 French cancer registries, 18%³ of the 1,000 patients in whom prostate cancer was diagnosed in 1995, presented locally advanced disease (T3 to T4).

However:

- The proportion of these patients with an indication for isolated hormone therapy is not known.
- There are no epidemiological data with which to evaluate the proportion of patients initially diagnosed at localised stages (T1, T2, N0) who subsequently progress to a locally advanced stage.

On the basis of these data, the target population of ENANTONE in this extension of indication is estimated to be 7,200 patients per year.

4.5. Transparency Committee recommendations

The Transparency Committee recommends inclusion on the list of medicines approved for use by hospitals and various public services in the new indication and at the posology of the marketing authorisation.

4.5.1. Packaging: Appropriate for the prescription conditions

4.5.2. Reimbursement rate: 100%

² Evolution de l'incidence et de la mortalité par cancer en France de 1978 à 2000 (INVS 2003)

³ Bauvin E, Soulié M, Ménégos F, Macé-Lesec'h J, Buémi A, Velten M, Villers A, Grosclaude P. Medical and non-medical determinants of prostate cancer management: a population-based study. Eur J Cancer. 2003;39:2364-71