HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

16 June 2010

YONDELIS 0.25 mg, powder for concentrate for solution for infusion B/1 (CIP code: 571 522-9)

YONDELIS 1 mg, powder for concentrate for solution for infusion B/1(CIP code: 571 524-1)

Applicant: PHARMA MAR S.A.

trabectedine
ATC code: L01CX01

List I
Medicine restricted to hospital use. Prescription is restricted to specialists in oncology or in haematology, or to physicians with competence in oncology. Medicine requiring special monitoring during treatment.

Orphan medicinal product status (30 May 2001)

Date of Marketing Authorisation (centralised European): 17 September 2007 – Variation of 28 October 2009

Reason for request: Inclusion on the list of medicines approved for hospital use in extension of indication “in combination with pegylated liposomal doxorubicin (PLD) in the treatment of platinum-sensitive recurring ovarian cancer”.

Medical, Economic and Public Health Assessment Division

1 CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient

trabectedine

1.2. Indications

“Yondelis is indicated for the treatment of patients with advanced soft-tissue sarcoma, after failure of anthracyclines and ifosfamide, or who are unsuited to receive these agents. Efficacy data are based mainly on liposarcoma or leiomyosarcoma.”

Yondelis in combination with pegylated liposomal doxorubicin (PLD) is indicated for the treatment of patients with relapsed platinum-sensitive ovarian cancer.”

1.3. Dosage

“The recommended dose of Yondelis in the treatment of ovarian cancer is 1.1 mg/m^2 body surface area as an infusion lasting 3 hours, immediately after administration of a dose of 30 mg/m^2 of PLD. In order to minimise the risk of reactions to the PLD infusion, the initial dose is administered at a rate not exceeding 1 mg/minute. If no adverse reaction to the infusion is observed, the PLD infusion can be continued for a duration of 1 hour (See also the Summary of Product Characteristics for PLD for specific recommendations concerning administration)."

2 SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification (2009)

L : Aantineoplastic and immunomodulating agents
L01 : Antineoplastic agents
L01C : Plant alkaloids and natural derivatives
L01CA : Other plant alkaloids and natural derivatives
L01CX01 : Trabectedine

2.2. Medicines in the same therapeutic category

2.2.1. Comparator medicines

None

2.3. Medicinal products with the same therapeutic aim

- CAELYX (doxorubicin)
- HYCAMTIN (topotecan)
- TAXOL (paclitaxel) and its generics
- CISPLATYL (cisplatin) and its generics
- PARAPLATIN (carboplatin) and its generics

3 ANALYSIS OF AVAILABLE DATA

The assessment of the therapeutic benefit of YONDELIS in the treatment of ovarian cancer is based on the OVA-301 pivotal study analysed below.

3.1. Efficacy

OVA-301 study

Open-label, randomised phase III study comparing the efficacy and tolerance of YONDELIS combined with pegylated liposomal doxorubicin (PLD) versus pegylated liposomal doxorubicin alone in patients with advanced relapsed ovarian cancer following first-line chemotherapy with platinum salts.
The patients were randomised to receive YONDELIS (1.,1 mg/m²) + PLD (30 mg/m²) every 3 weeks or PLD (50 mg/m²) every 4 weeks.

The primary endpoint was progression-free survival defined as the period between the date of randomisation and the date on which progression (clinical or radiological) was first observed, or the date of death from any cause.

Secondary endpoints:
- overall survival, defined as the interval between randomisation and death from any cause;
- overall response, defined as a complete response (disappearance of all lesions) or a partial response (reduction of at least 30% in the sum of the largest diameters of the lesions compared to baseline);
- CA-125 response, defined as a complete response (normalisation[1]) or a partial response with respect to the CA-125 tumour marker;
- quality of life
- tolerance.

Inclusion criteria included:
- age $\geq$ 18 years,
- patients with advanced ovarian cancer with treatment failure more than 6 months after the start of first-line chemotherapy based on platinum salts,
- patients with a platinum-resistant tumour or with a platinum-sensitive tumour, but who were ineligible for retreatment with platinum could be included.

Exclusion criteria included:
- patients treated with more than one prior chemotherapy regimen,
- refractory disease, defined as disease progression within 6 months of the beginning (first dose) of the initial line of platinum-based chemotherapy for ovarian cancer;

A disease is said to be chemosensitive if a response to first-line treatment results in a treatment-free interval of at least 6 months.
A disease is said to be chemoresistant if progression is observed during first-line therapy or the best response to therapy consists of stabilisation of the disease or relapse within 6 months following the completion of first-line treatment.

1 Value <35 U/ml

Results:

A total of 672 patients was randomised. The median age of the patients was 57 years and 97% of patients had remained in good general condition.
The metastatic sites at baseline (median of 2 lesions) were primarily the abdomen (74%), pelvis (69%), liver (29%) and lungs (18%).
First-line chemotherapy with platinum salts had failed in all patients: 64% had a platinum-sensitive tumour and 34% had a platinum-resistant tumour.

The principal analysis of progression-free survival was performed in 645 patients in whom the disease could be assessed and who underwent an independent radiological assessment.
According to an independent radiological analysis, progression-free survival was 7.3 months in the YONDELIS + PLD group versus 5.8 months in the PLD group, i.e. an absolute gain of 1.5 months (HR = 0.79, 95% CI [0.65-0.96], p = 0.0190).

There was no difference in median overall survival between the two groups: 22.4 months in the YONDELIS + PLD group versus 19.5 months in the group given PLD alone (HR = 0.85 IC 95% [0.70-1.03], p = 0.0920). Similar results were observed during the second interim analysis of overall survival performed following 419 of the 520 deaths (81%) required for the final analysis.

The rate of tumour response was 27.6% in the YONDELIS + PLD group versus 18.8% in the group given PLD alone. The median duration of the response did not differ between the two groups (7.9 months versus 7.7 months in the group given PLD alone).
The normalisation rate of CA-125 was 30% in the YONDELIS + PLD group versus 20% in the group given PLD alone.
No difference between the two groups was observed in the overall evaluation of quality of life.

A stratified analysis based on the sensitivity of patients to platinum showed the following results:
In the subgroup of patients with tumours sensitive to platinum (period of more than 6 months without platinum treatment), corresponding to the population specified in the MA (n = 417), progression-free survival was 9.7 months in the YONDELIS + PLD group versus 7.5 months in the group given PLD alone, namely an absolute gain of 2.2 months (HR- 0.73 95% CI [0.56-0.95], p = 0.0170).
In the subgroup of patients with tumours resistant to platinum (n = 228), there was no difference in progression-free survival between the two groups: 3.7 months with YONDELIS + PLD versus 4 months with PLD alone (HR = 0.95 95% CI [0.7-1.3]).

A post-hoc analysis was performed in a subgroup of patients with intermediate sensitivity to platinum (period of 6 to 12 months without platinum treatment). Since this was an exploratory analysis, the results will not be discussed.

Leukocyte growth factors were administered prophylactically more frequently to patients in the combination group (42%) than to those in the comparator group (27%).

3.2. Adverse effects

Treatment was discontinued due to adverse events in 23% of the YONDELIS + PLD group versus 15% of the group given PLD alone.
Grades 3 and 4 neutropenia was observed in 72% of the YONDELIS + PLD group versus 29.5% of the group given PLD alone. Febrile neutropenia was observed in 6.9% of the YONDELIS + PLD group versus 2.1% of the group given PLD alone.
Grades 3-4 thrombocytopenia was reported in 23.1% of the YONDELIS + PLD group versus 4.3% of the group given PLD alone.

Grades 3 and 4 elevation of alanine aminotransferase (ALT) was observed in 50.1% of the YONDELIS + PLD group versus 2.2% of the group given PLD alone.

3.3. Conclusion

The OVA-301 study included 672 patients who had already been treated for advanced ovarian cancer, with treatment failure more than 6 months after the start of first-line chemotherapy based on platinum. The population consisted of 64% patients with platinum-sensitive tumours and 36% with platinum-resistant tumours. This study compared a group treated with YONDELIS at a dose of 1.1 mg/m^2 combined with liposomal doxorubicin (PLD) at a dose of 30 mg/m^2, administered every 3 weeks with a group treated with PLD monotherapy at a dose of 50 mg/m^2 every 4 weeks.

In the population as a whole, according to an independent radiological analysis, the group given YONDELIS + PLD 30 mg/m^2, when compared to the group given PLD 50 mg/m^2 alone, showed:

- progression-free survival (primary endpoint) of 7.3 months versus 5.8 months, this being an absolute gain of 1.5 months (HR = 0.79 95% CI [0.65-0.96], p = 0.0190)
- a tumour response rate of 27.6% versus 18.8%
- a CA-125 normalisation rate of 30% versus 20%.

However, no difference was observed between the two groups with respect to:

- the median duration of the response: 7.9 months versus 7.7 months, p = 0.0920)
- median overall survival: 22.4 months versus 19.5 months
- overall assessment of the quality of life.

In the subgroup of patients with tumours sensitive to platinum (period of more than 6 months without platinum treatment), corresponding to the population specified in the MA (n = 417), progression-free survival in the YONDELIS + PLD30 mg/m^2 group was 9.7 months versus 7.5 months in the group given PLD 50 mg/m^2 alone, namely an absolute gain of 2.2 months (HR- 0.73 95% CI [0.56-0.95], p = 0.0170).

In the subgroup of patients with tumours resistant to platinum (n = 228), there was no difference in progression-free survival between the two groups: 3.7 months with YONDELIS + PLD versus 4 months with PLD alone (HR = 0.95 95% CI [0.7-1.3]).

Tolerance was poorer in the YONDELIS + PLD 30 mg/m^2 group compared to the group given PLD 50 mg/m^2 alone: toxicity was primarily haematological [grade 3-4 neutropenia (72% versus 29.5%) and grade 3-4 thrombocytopenia (23.1% versus 4.3%)] and hepatic [grade 3 and 4 elevation in ALT (50.1% versus 2.2%)].

4 TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit

Ovarian cancer is a serious and potentially life-threatening condition;
These proprietary products are intended for curative treatment;
It is a second-line treatment;

Public health benefit:

The incidence of ovarian cancer in France is estimated to be 4,440 new cases per year (InVs projections 2009). In 2005, this cancer ranked 5th for causes of death due to cancer in women, with 3,180 deaths per year, this being 2.2% of all deaths due to cancer. The public health burden of ovarian cancer is therefore significant. With respect to the subpopulation of patients with recurrent, platinum-sensitive ovarian cancer and likely to benefit from treatment with YONDELIS, this burden is moderate.

Improvement in the management and quality of life of cancer patients is a public health need which is included in the list of established priorities (Public Health Law 2004, Cancer Plan, Plan to improve quality of life of patients with chronic diseases).

In light of the available data, patients treated with YONDELIS combined with pegylated liposomal doxorubicin compared to those treated with pegylated liposomal doxorubicin alone benefit from a median gain of approximately 2 months in progression-free survival. Data on overall survival will only become interpretable in the final analysis of the pivotal study.

Furthermore, no improvement in quality of life was demonstrated in the pivotal study and an increase in haematological (grade 3 and 4 neutropenia and thrombocytopenia) and hepatic toxicity was noted in this same study.

The transferability of the results of the pivotal study to practice is acceptable.

Thus the proprietary product YONDELIS would not provide a supplementary response to the identified public health need.

YONDELIS is not expect to impact on the health system.

Consequently, taking account of these elements, a public health benefit is not to be expected from the use of YONDELIS in combination with pegylated liposomal doxorubicin.

The efficacy/adverse effects ratio of these proprietary products is moderate.
There are alternative drugs available;

The actual benefit of these products is substantial.

4.2. Improvement in actual benefit (IAB)

Taking into account the results of a subgroup analysis which showed an absolute gain of 2 months in progression-free survival with the combination of YONDELIS + pegylated liposomal doxorubicin versus pegylated liposomal doxorubicin alone, without an improvement in overall survival and at the cost of an increase in haematological and hepatic toxicity, the Committee considers that this combination does not provide an improvement in actual benefit (level V) within the therapeutic strategy.
YONDELIS + pegylated liposomal doxorubicin is a useful additional therapeutic means for the management of recurrent, platinum-sensitive ovarian cancer.

4.3. Therapeutic use

The standard treatment of advanced ovarian cancer is tumour cytoreductive surgery followed by 6 course of chemotherapy with a combination of a platinum salt (primarily carboplatin) and a taxane (usually paclitaxel).
At the end of this treatment, approximately two thirds of patients will show either a recurrence or a persistence of the lesion. In patients with a tumour considered to be sensitive to cisplatin (response to first-line treatment leading to a treatment-free period of at least 6 months), the initial treatment may be repeated and the result of this treatment is a median overall survival of ≥ 30 months. In patients with a tumour considered to be resistant to cisplatin (progression during first-line therapy or stabilisation of the disease or recurrence in the 6 months following completion of first-line treatment), the treatment is then changed; the median overall survival at this stage is approximately 8 months. Anthracyclines (in pegylated liposomal form), taxanes, topotecan and gemcitabine are used as monotherapy during these relapses. The published studies on repeat treatment with platinum salts mention a median period of progression-free survival of approximately 9 months[2].
In patients with ovarian cancer that is sensitive to platinum, but who are not eligible for repeat treatment with platinum salts, YONDELIS + pegylated liposomal doxorubicin is a useful additional therapeutic means for the management of this cancer.

4.4. Target population

The target population of YONDELIS consists of patients with platinum-sensitive, recurrent, advanced ovarian cancer, who are not eligible for repeat treatment with platinum salts due to platinum being contraindicated or because the patient has refused the treatment.
In the projections for the year 2009 made by the Institut de Veille Sanitaire [French Insitute for Public Health Surveillance], the incidence of ovarian cancer in France is estimated at 4,440 new cancer cases per year[3].
The advanced stages (III and IV) account for 75% of cases,[4] namely 3,330 patients per year.
Approximately two thirds[4] of patients, namely 2,200 patients per year, relapse within two years following first-line chemotherapy based on platinum salts and are candidates for second-line treatment. Approximately 80% of these patients have a platinum-sensitive tumour (expert opinion), namely 1,760 patients per year.
No data are available concerning the percentage of patients who are not eligible for repeat treatment with platinum salts; nevertheless, the experts estimate these would account for a maximum of 20%.
The target population for YONDELIS would therefore be a maximum of 350 patients per year.

4.5. Transparency Committee recommendations

The Transparency Committee recommends inclusion on the list of medicines approved for hospital use and various public services in this extension of indication.

2 Pisano C, Facchini G, Marchetti C, Pignata S. Treatment of recurrent epithelial ovarian cancer. Therapeutics and Clinical Risk Management 2009:5 421–426
3 http://www.invs.sante.fr/applications/cancers/projections2009/rapport_projections_nationales_cancer_2009.pdf
4 EPAR YONDELIS (28 October 2009)