HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

2 April 2008

YONDELIS 0.25 mg, vial containing powder for concentrate for solution for infusion
Box containing 1 vial (CIP: 571 522-9)
YONDELIS 1 mg, vial containing powder for concentrate for solution for infusion
Box containing 1 vial (CIP: 571 524-1)

Applicant: PHARMA MAR S.A.

trabectedin

ATC code: L01CX01

List I
Medicinal product for hospital use only. Prescription restricted to specialists in oncology or haematology, or doctors specialising in oncology. Medicinal product requiring specific monitoring during treatment.

Orphan medicinal product status

Date of marketing authorisation (centralised European procedure) issued "under exceptional circumstances[1]": 17 September 2007

Reason for request: Inclusion on the list of medicinal products approved for use by hospitals.

Medical, Economic and Public Health Assessment Division

1 This means that it was not possible to obtain full information about this proprietary medicinal product because of the rarity of this condition.

1 CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient

trabectedin

1.2. Indication

"Yondelis is indicated for patients suffering from evolutive soft tissue sarcoma in whom treatments based on anthracyclines and ifosfamide have failed, or who cannot take such medication. Most of the efficacy data has been obtained from patients suffering from liposarcoma and leiomyosarcoma."

1.3. Dosage

"The recommended dose is 1.5 mg/m^2 body surface area by intravenous infusion administered over the course of 24 hours every three weeks.

Treatment duration:
The number of cycles administered was not predetermined in the clinical trials. Treatment continued until a clinical benefit was obtained. Six or more cycles of trabectedin were administered to 168 out of 569 patients (29.5%) who were treated at the suggested dosage and regimen. This regimen was used for up to 38 cycles. No cumulative toxicity was observed in patients who underwent multiple cycles of treatment."

2 SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification (2007)

L: Antineoplastic and immunomodulating agents
L01: Antineoplastic agents
L01C: Plant alkaloids and natural products
L01CX: Other plant alkaloids and natural products
L01CX01: trabectedin

2.2. Medicines in the same therapeutic category

2.2.1. Comparator medicines

None

2.3. Medicines with a similar therapeutic aim

The following medicines, used alone or in the context of chemotherapy protocols:

- ADRIBLASTIN (doxorubicin)
- HOLOXAN (ifosfamide)
- DETICENE (dacarbazine)

3 ANALYSIS OF AVAILABLE DATA

The therapeutic benefit of Yondelis in the treatment of soft tissue sarcomas has been assessed on the basis of one pivotal study (ET743-STS-201).
Three non-comparative studies were provided in the application dossier. These studies were used as the basis for an application for a marketing authorisation for this proprietary drug submitted in 2001. The CHMP raised objections to their methodology[2]. They will therefore not be discussed in this document.

3.1. Efficacy

Study ET743-STS-201
Phase II, open-label, randomised controlled study assessing two dosages of Yondelis (every three weeks versus every week) administered to 270 patients suffering from locally advanced or metastatic liposarcoma or leiomyosarcoma whose condition had progressed or relapsed after treatment with at least anthracyclines and ifosfamide.

YONDELIS was administered at a dose of 1.5 mg/m^2 by intravenous infusion over 24 hours every three weeks or at a dose of 0.58 mg/m^2 by intravenous infusion over three hours once a week for three weeks in a four-week cycle.

Primary endpoint: time until progression of the disease, defined by the time between randomisation and the first documented progression of the disease or death following progression of the disease.

N.B.:This primary criterion was initially the response rate + stabilisation after six months. About a year after the start of the study, this endpoint was replaced by time until progression of the disease.

Secondary endpoints: overall survival, survival without progression, complete objective response rate and tolerance.

Results:
The demographic characteristics of both groups were similar: the average age was 53 (range from 20 to 80) and 63% of the patients were women. 66% of the patients had leiomyosarcoma and 34% had liposarcoma.
Most of the patients (96.7%) had already undergone surgery (median of three interventions in each group) and about 50% had undergone radiotherapy. All the patients had already had chemotherapy (median of two and three lines in each group): 99% had been treated both with anthracyclines and ifosfamide.

The time until progression of the disease was 3.7 months in the group receiving treatment once every three weeks versus 2.3 months in the group receiving treatment every week (p=0.0320).

The median progression-free survival time was 3.3 months in the group receiving treatment once every three weeks versus 2.3 months in the group receiving treatment every week (p=0.0418).

[2] www.emea.europa.eu/pdfs/human/opinion/570603en.pdf

There was no difference between the two groups with regard to median overall survival time: 13.9 months in the group receiving treatment once every three weeks versus 10.8 months in the group receiving treatment every week.
No complete response was observed. The "partial response + stable disease" rates were 44.7% in the group receiving treatment once every three weeks and 35.1% in the group receiving treatment every week.

3.2. Adverse events

The most common adverse events were:
- grades 3 or 4 neutropenia observed in about a quarter of cases
- thrombopenia: grade 3 (11%) and grade 4 (2%)
- increase in transaminase of grade 3 (approximately 40% of cases) and grade 4 (approximately 5% of cases).

The other adverse events were:
- severe hepatic toxicity: less than 1%
- grades 3 and 4 increase in CPK: 4%
- rhabdomyolysis: less than 1%

Other data
The company submitted indirect efficacy comparisons between Yondelis and ifosfamide or dacarbazine based on historic data observed in 146 patients suffering from soft tissue sarcoma in whom anthracycline-based treatment had failed (3 studies taken from the EORTC[3] database). The Committee notes that no appropriate statistical method was used for this retrospective analysis. This data is therefore not likely to provide sufficiently strong evidence and can therefore only be taken into consideration for descriptive or documentary purposes.

3.3. Conclusion

The therapeutic benefit of Yondelis was assessed by a phase II, open-label, randomised controlled study assessing two dosage schemes of Yondelis (every three weeks versus every week) administered to 270 patients suffering from locally advanced or metastatic liposarcoma or leiomyosarcoma whose condition had progressed or relapsed after treatment with at least anthracyclines and ifosfamide.
The time until progression of the disease (primary endpoint) was 3.7 months in the group receiving treatment once every three weeks versus 2.3 months in the group receiving treatment every week (p=0.0320).
The administration regimen specified in the marketing authorisation is the once every three weeks schedule.
The activity shown in the application dossier is minor and difficult to evaluate on the basis of the information provided: a small number of cases of "prolonged" stabilisation of the disease.
No data from comparative studies versus "supportive care" or a formalised comparison with a historic cohort is available; such data would have allowed the therapeutic contribution of this medication in this situation to have been assessed.
Limited safety data is available. The main risks that have been identified are haematological and hepatic toxicity.

3 European Organisation for Research and Treatment of Cancer

4 TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit

Soft tissue sarcomas, in particular liposarcoma and leiomyosarcoma, are serious conditions which affect patients' vital prognosis;
These proprietary products are intended for curative treatment;
This is a second-line treatment after failure of treatment with anthracyclines and ifosfamide;
The efficacy/adverse effects ratio for these medicinal products is high;
There is no validated alternative drug treatment at this stage of the disease;

Public health benefit:

Advanced soft tissue sarcomas (in particular liposarcomas and leiomyosarcomas) where treatment with anthracyclines and ifosfamide have failed or cannot be prescribed are serious conditions which can affect patients' vital prognosis, but which represent a minor public health burden because they are so rare.

The improved management of these conditions is a public health need coming within the scope of identified priorities (GTNDO[4], National rare diseases plan, absence of alternative treatments).

A review of the very limited data available (no formalised comparison with a historic cohort) shows that the expected impact of the proprietary medicinal product YONDELIS is difficult to quantify in these patients in terms of morbidity, mortality and quality of life. It is not possible to ascertain whether or not this proprietary drug meets an identified public health need.

Accordingly, in the current state of knowledge, this proprietary drug is not expected to have an impact on public health.

The actual benefit of these proprietary medicinal products is substantial.

4.2. Improvement in actual benefit

In the absence of data from studies versus "supportive care" or a formalised comparison with a historic cohort, it is impossible to assess the therapeutic contribution of this medication. Consequently, the Transparency Committee is of the opinion that in the current state of knowledge the proprietary medicinal product Yondelis does not offer any improvement in actual benefit (level V) in the management of patients suffering from liposarcoma or leiomyosarcoma in whom treatment based on anthracyclines and ifosfamide have failed.

4.3. Therapeutic use

Soft tissue sarcomas are relatively chemoresistant tumours for which a small number of effective chemicals are available: anthracyclines (mainly doxorubicin), ifosfamide and dacarbazine. These products are used alone or in combination in the metastatic phase of the disease. Response rates to first-line treatment range from 20 to 40%, with median survival rates of 12 to 15 months.
Several randomised studies have shown that:

- combinations without anthracyclines are less active than doxorubicin alone
- at equivalent doxorubicin dosages, the addition of a second product can lead to higher response rates but this is at the expense of greater toxicity and does not alter survival[5]

4 Groupe Technique National de Définition des Objectifs [National Technical Objective Definition Group] (DGS-2003)

5 Le Cesne A, Cioffi A. Chimiothérapie des sarcomes des tissus mous métastatiques et localement avancés [Chemotherapy of metastatic and locally advanced soft tissue sarcomas]. Oncol. 2007;9:114-125.

- sensitivity to chemotherapy varies according to histological sub-types: synovial sarcomas are particularly sensitive to ifosfamide; undifferentiated liposarcomas are the most chemosensitive; leiomyosarcomas are particularly sensitive to a gemcitabine/Taxotere combination; angiosarcomas are particularly sensitive to Taxol administered once a week.

No other drug has really been shown to be effective in patients who have unsuccessfully undergone treatment including doxorubicin and ifosfamide, either alone or in combination.
Chemotherapy is sometimes useful as a neoadjuvant treatment to render an evolutive tumour operable, but despite several randomised studies it has not been shown to be useful in an adjuvant situation.
Yondelis is a useful method of treatment in managing patients suffering from advanced liposarcoma or leiomyosarcoma in whom treatment based on anthracyclines and ifosfamide has failed.

4.4. Target population

The target population for YONDELIS is made up of patients suffering from advanced, metastatic or locally advanced liposarcoma or leiomyosarcoma in whom treatment with anthracyclines and ifosfamide has failed, or who cannot receive these products.

Very little epidemiological data is available because soft tissue sarcomas are rare cancers. The information obtained from the literature or presentations at conferences suggests that:

- it is estimated that there are 1,000 new cases a year in France[6]
- around 50% of patients experience local relapse or metastasis after initial local treatment[7]

Accordingly, it is estimated that the annual population of patients with evolutive soft tissue cancer is around 500 a year.
No precise data is available on the proportion of liposarcomas and leiomyosarcomas among soft tissue sarcomas.
The expert view is that 90% of patients with evolutive soft tissue sarcoma are treated by first-line chemotherapy, which is a monotherapy in 60% of cases.
About 75% of these patients will relapse and receive second-line chemotherapy.
According to these assumptions, the target population of YONDELIS is approximately 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.

6 FNCLCC. Standards, Options et Recommandations 2006 pour la prise en charge des patients adultes atteints de sarcome des tissus mous, de sarcome utérin ou de tumeur stromale gastro-intestinale 2006 Standards, Options and Recommendations for the management of adult patients suffering from soft tissue sarcoma, uterine sarcoma or gastrointestinal stromal tumours].
7 EPAR Yondelis (2007)