HAUTE AUTORITÉ DE SANTÉ

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TRANSPARENCY COMMITTEE

Opinion

24 July 2013

YONDELIS 0.25 mg, powder for concentrate for solution for infusion

Box of 1 vial (CIP: 571 522-9)

YONDELIS 1 mg, powder for concentrate for solution for infusion

Box of 1 vial (CIP: 571 524-1)

Applicant: Pharma Mar

INN	Trabectedin
ATC code (year):	L01CX01 (Alkaloids)
Reason for the request	**Re-assessment of the improvement in actual benefit at the company's request, in accordance with article R 163-12 of the Social Security Code.**
List(s) concerned	**Hospital use** (French Public Health Code L.5123-2)
Indication(s) concerned	**"Treatment of adult 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 and leiomyosarcoma patients."**

Actual Benefit	**The actual benefit remains substantial.**
Improvement in Actual Benefit	**In the absence of comparative data with an optimal level of evidence, the Committee considers that, on the current level of knowledge, YONDELIS offers no improvement in actual benefit (IAB V, nonexistent) in the treatment of adult patients with advanced soft-tissue sarcoma after failure of treatments based on anthracyclines and ifosfamide or in patients who are unsuited to receive these agents.**
Therapeutic use	**YONDELIS is a second-line treatment for soft-tissue sarcomas, after failure of chemotherapy including doxorubicin and ifosfamide, as monotherapy or in combination therapy, primarily for liposarcomas and leiomyosarcomas.**

01 ADMINISTRATIVE AND REGULATORY INFORMATION

Marketing Authorisation (centralised)	Initial Marketing Authorisation: 17 September 2007 (soft-tissue sarcomas) granted under exceptional circumstances.[1] In May 2012, this Marketing Authorisation was confirmed without time limit on its five-year renewal. Revised on 28 October 2009 (extension of the indication to the ovary)
Prescribing and dispensing conditions/special status	Orphan drug status (30 May 2001) List I Initial hospital prescription for six months, with renewal restricted to haematologists, oncologists, internal medicine specialists and gastroenterologists.

ATC Classification	2012 L: Antineoplastic and immunomodulating agents L01: Antineoplastic agents L01C: Plant alkaloids and other natural products L01CX: Other plant alkaloids and natural products L01CX01: Trabectedin

02 BACKGROUND

In September 2007, YONDELIS (trabectedin) was granted centralised Marketing Authorisation for the treatment of advanced soft-tissue sarcomas after failure of treatments based on anthracyclines and ifosfamide or in patients unsuited to receive these agents. Efficacy data are based mainly on liposarcoma and leiomyosarcoma patients.

In its Opinion of 2 April 2008, the Transparency Committee considered that the actual benefit of YONDELIS was substantial and that, in the absence of any study versus "supportive care" or formalised comparison with a historical cohort, it is not possible to assess the therapeutic benefit of this medicinal product. The Transparency Committee therefore considers that, on the current level of knowledge, the proprietary medicinal product YONDELIS offers no improvement in actual benefit in treatment.
Overall, the Committee recommends reimbursement of these proprietary medicinal products in the treatment of soft-tissue sarcomas.

In addition, the second indication of YONDELIS, in the treatment of ovarian cancer, was the subject of a Committee Opinion dated 16 June 2010.

This document is based on the analysis of new clinical data supplied by the company, which has requested re-assessment of the improvement in actual benefit in the indication advanced soft-tissue sarcoma.

[1] This means that, because of the rarity of this disease, it has not been possible to obtain complete information on this proprietary medicinal product.

03 THERAPEUTIC 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 and leiomyosarcoma patients.

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

04 DOSAGE

The recommended dose for the treatment of soft-tissue sarcoma is 1.5 mg/m^2 body surface area as an intravenous infusion over a period of 24 hours, every three weeks.

05 THERAPEUTIC NEED

Soft-tissue sarcomas (STS) are rare, accounting for fewer than 1% of all malignancies in adults. They are a heterogeneous group of cancers of the connective tissues formed from mesenchymal cells and their precursors. There are a number of histopathological STS subtypes.
At the localised stage, treatment is based primarily on surgery and radiotherapy. For control of the primary tumour and prevention of local recurrence, it is necessary to first carry out complete surgical resection, which must also aim to preserve function. The role of chemotherapy in adjuvant treatment is controversial.
At the metastatic stage, treatment is based on systemic chemotherapy. Soft-tissue sarcomas respond poorly to chemotherapy and only few of the available drugs are effective against such tumours: anthracyclines, primarily doxorubicin, ifosfamide, and dacarbazine. These products are used alone or in combination in the metastatic stage of the disease; percent response rates in first-line treatments vary from 20 to 40%, with median survival times of 12 to 18 months.
Numerous randomised studies have allowed us to establish that:

- combinations without anthracyclines are less active than doxorubicin on its own.
- at the equivalent dose of doxorubicin, combination with a second product sometimes gives better percent response rates, but at the cost of much higher toxicity and with no improvement in survival.
- sensitivity to chemotherapy varies according to histological type: synovial sarcomas show particular sensitivity to ifosfamide, undifferentiated liposarcomas respond the best to chemotherapy, leiomyosarcomas are particularly sensitive to a combination of gemcitabine and docetaxel, angiosarcomas show particular sensitivity to weekly paclitaxel.

After failure of treatment including doxorubicin and ifosfamide as monotherapy or in combination, trabectedin has Marketing Authorisation in this situation and, more recently, pazopanib (VOTRIENT) was granted Marketing Authorisation in sarcomatous tumours not including liposarcomas and GIST (gastrointestinal stromal tumours).

06 CLINICALLY RELEVANT COMPARATORS

06.1 Medicinal products

VOTRIENT from Glaxo-SmithKline has Marketing Authorisation in soft-tissue sarcomas not including liposarcoma and GIST.

Conclusion

The relevant comparator is VOTRIENT, except in tumours of liposarcoma and GIST histological type. In these cases, there is no relevant comparator.

07 INTERNATIONAL INFORMATION ON THE MEDICINAL PRODUCT

Country	REIMBURSEMENT	
	YES/NO If no, why not	Population(s) That of the Marketing Authorisation or restricted
Germany	yes	Marketing Authorisation Population
Belgium	yes	same
Italy	yes	same
Netherlands	yes	Leiomyosarcomas or myxoid liposarcomas
Spain	yes	Marketing Authorisation Population
Austria	yes	Marketing Authorisation Population
United Kingdom	yes	Marketing Authorisation Population

08 SUMMARY OF PREVIOUS ASSESSMENTS

Date of Opinion (reason for request)	2 April 2008
Indication	"Yondelis is indicated for the treatment of patients with advanced soft tissue sarcoma, after failure of anthracyclines or ifosfamide, or who are unsuited to receive these agents. Efficacy data are based mainly on liposarcoma and leiomyosarcoma patients."
Actual benefit (wording)	Substantial
Improvement in actual benefit (wording)	"In the absence of any study versus "supportive care" or formalised comparison with a historical cohort, it is not possible to assess the therapeutic benefit of this medicinal product. The Committee therefore considers that, on the current level of knowledge, the proprietary medicinal product YONDELIS offers no improvement in actual benefit (level V) in the treatment of patients with liposarcoma or leiomyosarcoma, after failure of treatment based on anthracyclines or ifosfamide."
Studies requested	None

09 ANALYSIS OF AVAILABLE DATA

The sole prospective study (pivotal study ET743-STS-201) available for evaluation of the efficacy of treatment with YONDELIS was examined by the Transparency Committee in its Opinion of 2 April 2008.

The new data submitted by the company for re-assessment of the IAB are:
- comparisons of observational data with those of the sarcomas register of the Rhône-Alpes region (patients untreated with YONDELIS):
    - retrospective collection of TUA data
    - retrospective collection of data on all patients treated with YONDELIS for advanced soft-tissue sarcoma as per the Marketing Authorisation, from 2008 to 2011 (Rétrospectyon);
    - a SAR-3002 cohort study.

These new observational data submitted do not permit demonstration of the efficacy of YONDELIS on overall survival and progression-free survival in the treatment of advanced soft-tissue sarcomas. Consequently, they are not detailed in this document.

- an indirect comparison of the results of the YONDELIS pivotal study STS-201 already assessed by the Transparency Committee versus historical data, obtained from an EORTC[2] database, of 79 patients treated with monotherapy in several phase II studies.

09.1 Efficacy

A/ Summary of the clinical data assessed in the TC Opinion of 2 April 2008:

The assessment of the therapeutic benefit of YONDELIS is based on one randomised, open-label phase II study that evaluated two YONDELIS dosage regimens, either once every three weeks or once a week, in 270 patients with locally advanced or metastatic liposarcoma or leiomyosarcoma in whom the disease had progressed or recurred after treatment with at least anthracyclines and ifosfamide.
The time to disease progression (primary efficacy endpoint) was 3.7 months in the group treated once every 3 weeks versus 2.3 months in the group treated once a week (p = 0.0320).
The once-every-3-weeks dosage regimen was the one specified in the Marketing Authorisation.
The efficacy of trabectedin is modest and difficult to assess based on some cases where the disease had stabilised for “long” periods.
There is no comparative study versus “supportive care” or formalised comparison with a historical cohort that allows the therapeutic benefit of this medicinal product in this situation to be assessed.
Safety data are limited. The principal risks identified are haematological and hepatic toxicity.

[2] European Organisation for Research and Treatment of Cancer

B/ New data submitted by the company

Indirect comparison of the results of YONDELIS pivotal study STS-201 versus historical data from the EORTC database:

The assessment comprises an indirect comparison after propensity score matching on progression-free survival and overall survival between the pivotal study subgroup (patients treated at a dosage of 1.5 mg/m^2 every 3 weeks, n = 136) and historical data of 79 patients with liposarcoma or leiomyosarcoma obtained from an EORTC database and taken from phase II studies of antimitotic drugs given as monotherapy (ifosfamide, dacarbazine and etoposide) in the second-line treatment of soft-tissue sarcomas.

The following points should be stressed:
- The submitted indirect comparison concerns the results of treatment with ifosfamide, whereas the indication of the Marketing Authorisation of YONDELIS concerned patients who do not respond to ifosfamide or who are unable to be treated with it.
- The propensity score is generally used to assess the efficacy of treatments in similar groups as regards which factors in particular led to one treatment being prescribed rather than another (after matching or stratification or through propensity score adjustment). Although this approach is in theory essentially correct as regards confounding factors examined, it fails to take account of other factors, which are disregarded in some cases and for the most part unknown. Whereas randomisation might be expected to achieve a balanced distribution of these unknown factors in each arm, non-random allocation of treatments provides no guarantee of this at all, even after use of the propensity score (or of a regression model).
The basic idea of the propensity score in its original form is that it allows the study group to be compared with a control group in a number of strata, each stratum being defined by the propensity to receive e.g. the study treatment, in particular for “strata” of patients with a low probability of using the study treatment instead of the comparison treatment. However, the patients who received the study treatment had been treated with it for specific reasons and these patients are therefore likely to differ from patients from the comparison group in the same stratum. The same is true of strata with a high probability of receiving the treatment.
Ultimately, in contrast to a double-blind trial, the use of a propensity score in an epidemiological (open-label) study does not allow us to eliminate measurement bias (the latter is however less acute when the clinical objective concerns a very clear-cut outcome such as overall survival, but potentially remains for a criterion such as progression-free survival).

Since these data are not likely to allow any conclusions to be drawn with a sufficient level of evidence, they cannot be taken into account in quantifying the efficacy of YONDELIS in this indication.

09.2 Safety/Adverse effects

Pharmacovigilance report – France (December 2007 to December 2011)

The population exposed to YONDELIS during the period from 17 September 2007 to 31 December 2011 (four years and three months) for the treatment of soft-tissue sarcomas or ovarian cancer (in combination with CAELYX) was estimated on the basis of sales for each indication, recommended doses in the treatment of soft-tissue sarcomas or ovarian cancer (for a mean body surface area (BSA) of 1.8 m^2), and mean number of observed cycles (3 for soft-tissue sarcomas, 5.5 for ovarian cancer). Based on these estimates, 2440 patients were treated with YONDELIS in France during this period.

During this period, there were 57 declared cases (spontaneous reports) comprising 157 AEs, of which 137 were serious adverse events (SAEs) and 20 non-serious. The outcome was fatal for 8 patients (19 AEs), 57 AEs resolved, 16 had not resolved by the time of the report, and the course was not known for 65 AEs.

The overall incidence of the 157 AEs was 6.43%. The distribution of AEs according to organ system class (OSC) is given in Table 1.

Table 1: Adverse events spontaneously reported in France (17 September 2007 to 31 December 2011) by organ system class (estimated number of patients: 2440)

Designation by OSC	Number of AEs (n = 157)	Incidence
General disorders and administration site conditions	30	1.23%
Hepatobiliary disorders	29	1.19%
Blood and lymphatic system disorders	18	0.74%
Investigations	15	0.61%
Gastrointestinal disorders	13	0.53%
Cardiac disorders	9	0.36%
Injury, poisoning and procedural complications	7	0.29%
Respiratory, thoracic and mediastinal disorders	6	0.24%
Vascular disorders	6	0.24%
Osteoarticular and systemic disorders	4	0.16%
Nervous system disorders	4	0.16%
Congenital, familial and genetic disorders*	3	0.12%
Infections and infestations	3	0.12%
Metabolism and nutrition disorders	3	0.12%
Skin and subcutaneous tissue disorders	3	0.12%
Renal and urinary disorders	2	0.08%
Endocrine disorders	1	0.04%
Neoplasms benign, malignant and unspecified	1	0.04%
TOTAL	**157**	**6.43%**

*: Three events were reported under the term “aplasia” (used in France to refer to bone marrow suppression), which corresponds to this OSC designation in MedDRA.

The frequency, nature and seriousness of reported events are in line with the known safety profile of YONDELIS and do not constitute a safety signal.

09.3 Usage/prescription data

The data on the characteristics of the population treated with YONDELIS for soft-tissue sarcoma are obtained from compassionate use programmes and are summarised as follows:

- the treated population is primarily female, aged 60 years or under, with leiomyosarcoma (30-36%), liposarcoma (approx. 20%) or synovial sarcoma (approx. 10%), and with metastatic sarcoma (80%) at the start of treatment with YONDELIS.
- YONDELIS was given mostly as second-line (40%) and third-line (40%) chemotherapy.

Usual duration of treatment:
- The median number of cycles given is three or four cycles; approximately 25% of patients received more than six cycles (TUA, retrospective Retrospectyon cohort).

Average dosage:
- The mean dosage per cycle in the SAR-3002 compassionate programme was 1258 mg/m^2.

Co-prescriptions:
- Premedication with dexamethasone.

09.4 Summary & discussion

In support of its application for re-evaluation of the IAB, the company has submitted comparisons of observational data that do not permit demonstration of the efficacy of YONDELIS on overall survival and progression-free survival in the treatment of advanced soft-tissue sarcomas.
The company has also submitted an indirect comparison of results of treatment with YONDELIS obtained in a pivotal study subgroup in particular (patients treated at a dosage of 1.5 mg/m^2 every 3 weeks, n = 136) versus historical data of 79 patients with liposarcoma or leiomyosarcoma obtained from an EORTC database and taken from phase II studies of antimitotic drugs given as monotherapy (ifosfamide, dacarbazine and etoposide) in the second-line treatment of soft-tissue sarcomas. However, this submitted indirect comparison concerns the results of treatment with ifosfamide, whereas the indication of the Marketing Authorisation of YONDELIS concerned patients who do not respond to ifosfamide or who are unable to be treated with it.

All in all, these new data do not allow any new conclusions to be drawn about the therapeutic benefit of YONDELIS in the treatment of advanced soft-tissue sarcomas after failure of treatments based on anthracyclines and ifosfamide. The sole prospective study (pivotal study ET743-STS-201) available for evaluation of the efficacy of treatment with YONDELIS remains the one examined by the Transparency Committee in its earlier Opinion of 2 April 2008.

010 THERAPEUTIC USE

At the localised stage, treatment of soft-tissue sarcoma is based primarily on surgery and radiotherapy. For control of the primary tumour and prevention of local recurrence, it is necessary to first carry out complete surgical resection, which must also aim to preserve function. The role of the chemotherapy given as adjuvant treatment is controversial.
At the metastatic stage, treatment is based on systemic chemotherapy.
Soft-tissue sarcomas respond poorly to chemotherapy and there is only a small number of drugs that are effective in their treatment: anthracyclines, primarily doxorubicin, ifosfamide, and dacarbazine. These products are used alone or in combination in the metastatic stage of the disease; percent response rates in first-line treatments vary from 20 to 40%, with median survival times of 12 to 18 months.
Numerous randomised studies have allowed us to establish that:
- combinations without anthracyclines are less active than doxorubicin on its own.
- at the equivalent dose of doxorubicin, combination with a second product sometimes gives better response rates, but at the cost of much higher toxicity and with no improvement in survival.
- sensitivity to chemotherapy varies according to histological type: synovial sarcomas show particular sensitivity to ifosfamide, undifferentiated liposarcomas respond the best to chemotherapy, leiomyosarcomas are particularly sensitive to a combination of gemcitabine and docetaxel, angiosarcomas show particular sensitivity to weekly paclitaxel.

After failure of treatment including doxorubicin and ifosfamide as monotherapy or in combination, trabectedin (YONDELIS) has Marketing Authorisation in this situation and, more recently, pazopanib (VOTRIENT) was granted Marketing Authorisation in the treatment of these tumours not including liposarcomas and gastrointestinal stromal tumours (GIST). There is as yet no available comparison between these two drugs.

011 TRANSPARENCY COMMITTEE CONCLUSIONS

In view of all the above information, and following the debate and vote, the Committee's opinion is as follows:

011.1 Actual benefit

◗ Soft-tissue sarcomas are serious pathologies that are life-threatening.
◗ These proprietary medicinal products are intended as specific curative cancer therapy.
◗ The efficacy/adverse effects ratio is high.
◗ There are few alternative drug therapies at this stage of the disease. In the case of liposarcoma, there are none.
◗ This is a second-line treatment after failure of chemotherapy based on anthracyclines and ifosfamide.

◗ Public health benefit:
Advanced soft-tissue sarcomas (particularly liposarcomas and leiomyosarcomas) refractory to or unable to benefit from treatment with anthracyclines or ifosfamide are serious pathologies that are life-threatening, but represent a low public health burden because of their rarity.
Improving the management of these diseases is a public health need that is an established priority (GTNDO[3], Rare Diseases Plan, lack of alternative treatments).
From the limited experimental data and comparisons of low methodological meaningfulness made on the basis of epidemiological data, the expected impact of the proprietary medicinal product YONDELIS on morbidity/mortality and quality of life in these patients is difficult to quantify. It is impossible to know whether or not this proprietary medicinal product meets an identified public health need.
In the current state of knowledge, the proprietary medicinal product is not expected to benefit public health.

Taking account of these points, the Committee considers that the actual benefit of YONDELIS remains substantial in the indication "Treatment of adult patients with advanced soft tissue sarcoma, after failure of anthracyclines and ifosfamide, or who are unsuited to receive these agents".

011.2 Improvement in actual benefit (IAB)

In the absence of comparative data with an optimal level of evidence, the Committee considers that, in the current state of knowledge, YONDELIS offers no improvement in actual benefit (IAB V, nonexistent) in the treatment of adult patients with advanced soft-tissue sarcoma after failure of treatments based on anthracyclines and ifosfamide or in patients who are unsuited to receive these agents.

[3] Groupe Technique National de Définition des Objectifs [National Technical Group for the Definition of Public-Health Objectives] (Directorate-General for Health 2003)

011.3 Target population

Based on the pivotal study (study ET743-STS-201), the target population of YONDELIS in this indication is patients with liposarcoma or leiomyosarcoma.
Sarcomas are rare tumours with an incidence of approximately 6 new cases per 100,000 individuals per year, which corresponds to approximately 4000 estimated new cases per year in France.[4]
Excluding GIST and osteosarcomas (approximately 1% of all cancers), this leaves 3600 cases of soft-tissue sarcoma per year.
Among soft-tissue sarcomas as a whole, the proportion of leiomyosarcomas is estimated at 11% and that of liposarcomas at 16%[5] (i.e. 972 patients per year).
The percentage of patients with recurrence or metastases after initial local treatment is about 50%[6] (i.e. 486 patients per year).
According to experts, approximately 90% of patients with advanced soft-tissue sarcoma are treated with first-line chemotherapy and approximately 75% will suffer recurrence and be eligible for second-line chemotherapy.
The target population for YONDELIS in this indication is estimated at around 350 patients per year.

[4] Verhaeghe JL, Rios M, Leroux A, Sirveaux F, Henrot P, Blum A, Marchal F. Traitement des sarcomes des tissus mous de l'adulte: quelle stratégie pour optimiser le traitement. e-mémoires de l'Académie Nationale de Chirurgie 2011; 10 (1): 048-053.
[5] Ducimetière F, Lurkin A, Ranchère-Vince D, et al. Incidence, épidémiologie des sarcomes et biologie moléculaire. Résultats préliminaires de l'étude EMS en Rhône-Alpes. Bull Cancer 2010; 97: 629-41.
[6] EPAR Yondelis (2007)