HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

29 April 2009

NAVELBINE 20 mg, soft capsules
B/1 (CIP: 365 948-4)

NAVELBINE 30 mg, soft capsules
B/1 (CIP: 365 949-0)

Applicant: PIERRE FABRE MEDICAMENT

Vinorelbine ditartrate

ATC code: L01CA04

List I
Medicine for hospital prescription only. Prescription restricted to oncology or haematology specialists or doctors with cancer training. Medicine requiring special monitoring during treatment.

Date of Marketing Authorisation (national): 22 February 2001

Date of revision of Marketing Authorisation: 14 March 2005 – 30 May 2008

Reason for request: Inclusion on the list of medicines reimbursed by National Health Insurance and approved for use by hospitals in the extension of indication “combination chemotherapy in non-small cell lung cancer”.

Note: The original wording for NAVELBINE in lung cancer was limited to single-agent chemotherapy.

Medical, Economic and Public Health Assessment Division

1 CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient

Vinorelbine ditartrate

1.2. Indications

"Oral navelbine is indicated as single-agent chemotherapy and **combination chemotherapy** in the treatment of:

- **non-small cell lung cancer**,
- metastatic breast cancer."

1.3. Dosage

"In combination chemotherapy:

The results of clinical studies demonstrate that an oral dose of 80 mg/m^2 corresponds to an IV dose of 30 mg/m^2 and that an oral dose of 60 mg/m^2 corresponds to an IV dose of 25 mg/m^2.

For combination regimens, the dose and treatment schedule are to be adapted on this basis.

Capsules of different dosages (20, 30, 40, 80 mg) are available so that the appropriate combination that achieves the desired dosage can be selected. The table below gives the required dose according to body surface area (BSA) range.

	60 mg/m^2	80 mg/m^2
BSA (m^2)	Dose [mg]	Dose [mg]
0.95 to 1.04	60	80
1.05 to 1.14	70	90
1.15 to 1.24	70	100
1.25 to 1.34	80	100
1.35 to 1.44	80	110
1.45 to 1.54	90	120
1.55 to 1.64	100	130
1.65 to 1.74	100	140
1.75 to 1.84	110	140
1.85 to 1.94	110	150
≥ 1.95	120	160

Even in the case of patients with a BSA ≥ 2 m^2, the total dose must never exceed 120 mg per week (60 mg/m^2 dosage) or 160 mg per week (80 mg/m^2 dosage)."

2 SIMILAR MEDICINAL PRODUCTS

2.1. ATC classification (2005)

L: Antineoplatic and immunomodulating agents
L01: Antineoplatic agents
L01C: Plant alcaloids and other natural products
L01CA: Vincaalcaloids and analogues
L01CA04: Vinorelbine

2.2. Medicines in the same therapeutic category

2.2.1. Comparator medicines

- NAVELBINE (10 mg, 50 mg), solution for injection in vial
- vindesine (ELDISINE)

2.3. Medicines with a similar therapeutic aim

- GEMZAR (gemcitabine)
- ALIMTA (pemetrexed)
- TAXOTERE (docetaxel)
- TAXOL (paclitaxel) and its generics
- ADRIBLASTINE (doxorubicin) and its generics
- ELDISINE (vindesine)
- ENDOXAN (cyclophosphamide)
- HOLOXAN (ifosfamide)
- AVASTIN (bevacizumab)
- CISPLATYL (cisplatin) and its generics
- PARAPLATIN (carboplatin) and its generics
- TARCEVA (erlotinib)

3 ANALYSIS OF AVAILABLE DATA

The dossier for the extension of the indication of NAVELBINE soft capsules from single-agent chemotherapy to combination chemotherapy in the treatment of non-small cell lung cancer is based on three non-comparative phase II studies (study CA 202 J1, study CA 206 J and study CA 201 J1).
The company has also supplied a phase III comparative study (study CA 301) that was not submitted to the market authorisation request of this extension of the indication.

3.1. Efficacy

Study CA 202 J1
Non-comparative phase II study evaluating the efficacy and tolerance of NAVELBINE (alternation of IV and oral forms) in combination with cisplatin in 56 patients with treatment-naïve, locally advanced or metastatic (stage IIIb and IV) non-small cell lung cancer.
The primary endpoint was the objective response rate (partial and complete).
Secondary endpoints were the duration of response, progression-free survival, and median overall survival.

The objective response (partial[1] + complete[2]) to treatment was evaluated according to the RECIST (Response Evaluation Criteria in Solid Tumors[3, 4]) criteria.

Treatments (4-week cycles):
- day 1: NAVELBINE IV 25 mg/m^2 followed by cisplatin 100 mg/m^2
- days 8, 15 and 22: NAVELBINE oral 60 mg/m^2

Results:
The median age of the patients was 60 years.
The overall response rate was 30.4%, composed entirely of partial responses. The median duration of response was 8 months.
The median progression-free survival was 5.5 months and the median overall survival was 8.9 months.

Study CA 206 J1
Non-comparative phase II study evaluating the efficacy and tolerance of oral NAVELBINE given in combination with cisplatin followed by oral NAVELBINE alone in 56 patients with treatment-naïve, locally advanced or metastatic (stage IIIb and IV) non-small cell lung cancer.
The primary endpoint was the overall response rate.
Secondary endpoints were the duration of response, progression-free survival, and median overall survival.

[1] Partial response: defined as at least a 30% decrease in the sum of the longest diameters of each target lesion, taking as reference the baseline sum of the longest diameters.
[2] Complete response: defined as disappearance of all target lesions
[3] James K, Eisenhauer E, Christian M et al. Measuring response in solid tumors: unidimensional versus bidimensional measurement. J Natl Cancer Inst 1999; 91: 523-8
4 Therasse P, Arbuck S, Eisenhauer E et al. New Guidelines to Evaluate the Response to Treatment in Solid Tumors. J Natl Cancer Inst 2000; 92: 205-16

Treatments (3-week cycles):

Cycle 1:
- day 1: NAVELBINE oral 60 mg/m^2 + cisplatin 80 mg/m^2
- day 8: NAVELBINE oral 60 mg/m^2

Cycles 2 to 4:
- day 1: NAVELBINE oral 80 mg/m^2 + cisplatin 80 mg/m^2
- day 8: NAVELBINE oral 80 mg/m^2

Cycle 5 and beyond (if showing response or stabilisation):
- days 1, 8 and 15: NAVELBINE oral 80 mg/m^2

Treatment was continued until progression or unacceptable toxicity.

Results:
The median age was 60.4 years.
The overall response rate was 25%, composed entirely of partial responses. The median progression-free survival was 4 months and the median overall survival was 10 months.

Study CA201 J1

Non-comparative phase II study evaluating the efficacy and tolerance of NAVELBINE (alternation of IV and oral forms) in combination with carboplatin in 52 patients with treatment-naïve, locally advanced or metastatic (stage IIIb and IV) non-small cell lung cancer.

The primary endpoint was the overall response rate.
Secondary endpoints were the duration of response, progression-free survival, and median overall survival.

Treatments (3-week cycles):
- day 1: NAVELBINE IV 25 mg/m^2 followed by carboplatin AUC 5
- day 8: NAVELBINE oral 60 mg/m^2

Results:
The median age of the patients was 62 years.
The overall response rate was 15.4%, composed entirely of partial responses. The median duration of response was 7.9 months.
The median progression-free survival was 5.1 months and the median overall survival was 9.3 months.

Study CA 301 J1

Randomised comparative phase III study evaluating the efficacy and tolerance of NAVELBINE (alternation of IV and oral forms) versus docetaxel in combination with carboplatin, in 390 patients with treatment-naïve, locally advanced or metastatic (stage IIIb and IV) non-small cell lung cancer.

The primary endpoint was the time to treatment failure[5].
Secondary endpoints were the objective response rate according to the RECIST criteria, overall survival, and quality of life evaluated by the EORTC questionnaires (QLQ-C30 and QLQ-LC13).

Treatments (3-week cycles) were:

- NAVELBINE-cisplatin combination:
  - day 1: NAVELBINE IV 25 mg/m^2 followed by cisplatin 80 mg/m^2
  - day 8: NAVELBINE oral 60 mg/m^2

  In the absence of grade 3 or 4 haematotoxicity, the NAVELBINE dosage was increased from the second cycle:
  - day 1: NAVELBINE IV 30 mg/m^2 followed by cisplatin 80 mg/m^2
  - day 8: NAVELBINE oral 80 mg/m^2

- docetaxel-cisplatin combination:
  - day 1: docetaxel IV 75 mg/m^2 followed by cisplatin 75 mg/m^2

Results:

The median age of the patients was 59.4 years in the NAVELBINE group and 62.1 years in the docetaxel group. In the two groups, 83% of patients were at the metastatic stage.
Squamous-cell carcinoma was found in about one third of cases.
The ITT analysis covered 381 of the 390 patients in the study.

The time to treatment failure (primary endpoint) was 3.22 months in the NAVELBINE group versus 4.11 months in the docetaxel group ($p = 0.2$).
There was no observed difference between the two groups regarding the following secondary endpoints:
- overall response rate (31.2% in the NAVELBINE group versus 29.6% in the docetaxel group);
- median progression-free survival (4.9 months in the NAVELBINE group versus 5.1 months in the docetaxel group);
- median overall survival (9.9 months in the NAVELBINE group versus 9.8 months in the docetaxel group);
- quality of life.

[5] defined as the length of time between randomisation and one of the following events: progression or recurrence of the tumour, death irrespective of cause, initiation of another anticancer therapy

3.2. Adverse effects

The tolerance data arise from the comparative phase III study.
The incidence of grades 3-4 neutropenia was 52.7% in the NAVELBINE group and 56.6% in the docetaxel group. Febrile neutropenia was observed in 8.9% of cases in the NAVELBINE group and in 4.2% of cases in the docetaxel group.
The incidence of grades 3-4 anaemia was 13.9% in the NAVELBINE group and 3.7% in the docetaxel group.
The incidence of grades 3-4 vomiting was 9.4% in the NAVELBINE group and 5.8% in the docetaxel group.

3.3. Conclusion

The extension of indication dossier of NAVELBINE capsules from single-agent chemotherapy to combination chemotherapy in the treatment of advanced-stage non-small cell lung cancer is based on three non-comparative phase II studies evaluating the efficacy and tolerance of oral NAVELBINE in combination with a platinum salt (cisplatin or carboplatin). The observed overall response rate (primary endpoint) was 15 to 30% according to study and the median overall survival was 8.9 to 10 months.
The Committee stresses that these results were observed in studies (2 out of 3) where NAVELBINE was used in both the oral and IV forms at the same patients.
In the randomised phase III study in which the principal objective was to establish the superiority of NAVELBINE versus docetaxel, in combination with cisplatin, the efficacy results in the two groups were similar, in particular the median overall survival of almost 10 months in each group (9.9 months in the NAVELBINE group versus 9.8 months in the docetaxel group).
Grades 3 to 4 adverse events reported more frequently in the NAVELBINE group than in the docetaxel group were febrile neutropenia (8.9% vs. 4.2%), anaemia (13.9% vs. 3.7%) and vomiting (9.4% vs. 5.8%).

4 TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit

Non-small cell lung cancer (NSCLC) is a life-threatening disease;
These proprietary products are intended for curative treatment;
The efficacy/adverse effects ratio is high;
It is a first-line treatment;
There are alternative drugs available;

Public health benefit:

The public health burden of non-small cell lung cancer (NSCLC) is high.
The availability of new therapeutic options for the treatment of lung cancer is a public health need.
The oral capsule form of NAVELBINE is not expected to have any additional impact on morbidity and mortality compared with the IV form. Moreover, on the basis of the available data it is not possible to assess the impact on quality of life.
Consequently, the capsule form of NAVELBINE is not expected to offer any additional benefit to public health over the IV form.

The actual benefit is substantial.

4.2. Improvement in actual benefit (IAB)

NAVELBINE soft capsules do not provide any improvement in actual benefit in the standard treatment of non-small cell lung cancer.

4.3. Therapeutic use

Surgery is the treatment of choice in the early stages of NSCLC. However, a large proportion of patients are diagnosed at an advanced stage of the disease (about 30% at the locally advanced stage and 40% at the metastatic stage), and the early stage accounts for only about 25 to 30%.
The standard first-line treatment for patients with advanced-stage disease consists of dual therapy based on a platinum salt (cisplatin or carboplatin) in combination with gemcitabine or vinorelbine or docetaxel or paclitaxel. Pemetrexed is reserved for the non-squamous cell histological form.
The one-year survival rate reported for these treatments was 31% to 46% depending on the study[6]. A doublet of chemotherapy based on a platinum salt seems to increase overall survival and the time to treatment failure by about 2 months in comparison with cisplatin monotherapy[7,8]. Antiangiogenic therapy can be combined with chemotherapy in the non-squamous histological form.
Oral NAVELBINE constitutes an alternative to the intravenous form primarily on day 8 of the treatment regimen when given in combination with a platinum salt.

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[6] Suresh Ramalingam and Chandra P. Belani. Systemic Chemotherapy for Advanced Non-Small Cell Lung Cancer: Recent Advances and Future Directions. The Oncologist 2008; 13 (suppl. 1): 5-13.

7 Wozniak AJ, Crowley JJ, Balcerzak SP, et al. Randomized trial comparing cisplatin with cisplatin plus vinorelbine in the treatment of advanced non-small cell lung cancer: A Southwest Oncology Group study. J Clin Oncol. 1998; 16: 2459-2465

8 Sandler A. B, Nemunaitis J, Denham C, et al. Phase III Trial of Gemcitabine Plus Cisplatin Versus Cisplatin Alone in Patients With Locally Advanced or Metastatic Non-Small Cell Lung Cancer. Journal of Clinical Oncology 2000:18 :122

4.4. Target population

The target population of NAVELBINE consists of patients with locally advanced or metastatic (IIIB and IV) non-small cell lung cancer eligible for first-line chemotherapy.
The information used to calculate this population is as follows:
The most recent estimate of the incidence of lung cancer in France was conducted in 2005 by the National Institute for Public Health Surveillance [InVS] and the FRANCIM network, recording 30,650 new cases per year (InVS, 2008).
Of these, 80 to 85% are non-small cell cancers (KBP French lung-cancer cohort followed up in 2000) (Blanchon, 2002), i.e. 25,440 new cases per year.
At initial diagnosis of the disease, it is estimated that:
- 65% (16,536 patients) are inoperable stage IIIB and IV cases,
- 35% (8904 patients) are patients with advanced localised cancer eligible for initial treatment with surgery or radiotherapy, but that 2 out of 5 will suffer from a recurrence (3560 patients) and will be eligible for systemic therapy.

Thus, approximately 20,000 patients each year are potentially eligible for first-line treatment of locally advanced or metastatic lung cancer.

4.5. Transparency Committee recommendations

The Transparency Committee recommends inclusion on the list of medicines reimbursed by National Health Insurance and on the list of medicines approved for use by hospitals and various public services in this extension of indication.

4.5.1. Packaging: the packaging is appropriate for the prescription conditions.

4.5.2. Reimbursement rate: 100%