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 metastatic breast cancer”.

Note: The original wording for NAVELBINE in metastatic breast 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
- ELDISINE (vindesine)
- VELBE (vinblastine)

2.3. Medicines with a similar therapeutic aim

Anthracyclines:
- ADRIBLASTINE (doxorubicin) and medicinal products containing doxorubicin
- FARMORUBICINE (epirubicine)

Other intercalating agents:
- NOVANTRONE (mitoxantrone)

Alkylating agents:
- ENDOXAN-ASTA (cyclophosphamide)
- AMETYCINE C (mitomycin)
- HOLOXAN (ifosfamide)

Antimetabolites:
- FLUOROURACIL ICN (fluorouracil) and medicinal products containing fluorouracil
- LEDERTREXATE (methotrexate) and medicinal products containing methotrexate

Pyrimidine analogues:
- GEMZAR (gemcitabine)

Taxanes:
- TAXOL (paclitaxel)
- TAXOTERE (docetaxel)

Podophyllotoxin derivatives:
- VEPESID SANDOZ (etoposide)

Monoclonal antibodies:
HERCEPTIN (trastuzumab), in HER2-positive tumours only.
AVASTIN (bevacizumab)

Hormone therapy used in the treatment of metastatic breast cancer.

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 metastatic breast cancer is based on four non-comparative studies that evaluated the efficacy and tolerance of oral NAVELBINE in combination with epirubicin (study CA 205 B0), docetaxel (study CA 101 B0), paclitaxel (study CA 102 B0) and capecitabine (study CA 103 B0).

3.1. Efficacy

Study CA 205 B0

This is a non-comparative phase II study that evaluated the efficacy and tolerance of NAVELBINE (alternation of IV and oral forms) in combination with epirubicin in 49 patients with treatment-naïve metastatic breast 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 epirubicin 90 mg/m^2
- day 8: NAVELBINE oral 60 mg/m^2

Results:
The median age was 54.9 years.
The overall response rate[1] was 51%, composed primarily of partial responses (46.9%). The median duration of response was 8.5 months.
The median progression-free survival was 8.4 months and the median overall survival was 14.5 months.

Study CA 101 B0

This is a non-comparative phase II study that evaluated the efficacy and tolerance of NAVELBINE in combination with docetaxel in 49 patients with treatment-naïve metastatic breast 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 20 mg/m^2 and docetaxel 60 mg/m^2
- day 15: NAVELBINE oral 60 mg/m^2

Results:
The median age of the patients was 53.8 years.
The overall response rate was 48.9%, composed primarily of partial responses (46.9%). The median duration of response was 9.4 months.
The median progression-free survival was 5.5 months and the median overall survival was 33.2 months.

[1] Including both complete (disappearance of the tumour) and partial (over 50% reduction in tumour size) responses

Study CA102 B0

This non-comparative phase II study evaluated the efficacy and tolerance of NAVELBINE in combination with paclitaxel in 48 patients with treatment-naïve metastatic breast 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):
- NAVELBINE oral 80 mg/m^2 (day 1 and day 15)
- paclitaxel 110 mg/m^2 (day 1)

Results:
The median age of the patients was 51.9 years.
The overall response rate was 33.3%, composed entirely of partial responses. The duration of response was not calculated.
The median progression-free survival was 5 months and the median overall survival was 28 months.

Study CA 103 B0

This non-comparative phase II study evaluated the efficacy and tolerance of NAVELBINE in combination with capecitabine in 52 patients with treatment-naïve metastatic breast 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):
- NAVELBINE oral 60 mg/m^2 (days 1, 8 and 15)
- capecitabine 2000 mg/m^2 (day 1 to day 14)

Results:
The median age was 59.9 years.
The overall response rate was 44.2%, composed primarily of partial responses (40.4%). The duration of response was not calculated.
The median progression-free survival was 8.4 months and the median overall survival was 25.8 months.

3.2. Adverse effects

The principal adverse events observed in the four phase II studies were grade 3-4 neutropenia in more than a half of cases (46.2% to 77.1%), with a low incidence of febrile neutropenia (1.9% to 8.2%), and diarrhoea (14.3% to 67.3%), a low incidence of grades 3-4, below 7% (1.9% to 6.3%).

3.3. Conclusion

The extension of indication dossier of NAVELBINE, oral form, from single-agent chemotherapy to combination chemotherapy in the treatment of metastatic breast cancer is based on four non-comparative phase II studies that evaluated the efficacy and tolerance of oral NAVELBINE in combination with epirubicin (study CA 205 B0), docetaxel (study CA 101 B0), paclitaxel (study CA 102 B0) and capecitabine (study CA 103 B0).
The observed overall response rate (primary endpoint) was 33.3 to 51%.
The Committee stresses that these results were observed in studies (2 out of 4) where NAVELBINE was used in both the oral and IV forms in the same patients.
The principal adverse events observed in the four phase II studies were grade 3-4 neutropenia and diarrhoea, occurring in about half of cases.
The absence of any comparison with combinations used as first-line treatment of breast cancer prevents an exact appraisal of the efficacy of this product.

4 TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit

Breast cancer is a life-threatening disease;
The product is 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 breast cancer is high. The burden relating to the subset of patients with metastatic breast cancer is substantial.
The availability of new therapeutic options for the treatment of metastatic breast 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 of this proprietary drug is substantial.

4.2. Improvement in actual benefit (IAB)

NAVELBINE soft capsules do not provide any improvement of the actual benefit for the standard treatment of metastatic breast cancer (IAB V).

4.3. Therapeutic use

The first-line treatment of metastatic breast cancer depends on:

- the time interval between adjuvant therapy and first-line metastatic treatment (< 6 months, between 6 months and 1 year, > 1 year),
- whether hormone receptors and/or HER2 overexpression are present,
- the type of metastases: number of sites, size or localisation (visceral in particular),
- the patient's general condition,
- the type of adjuvant therapy.

1/ In the absence of poor prognostic factors and if hormone receptors are present, the first-line treatment is hormone therapy.
2/ In the presence of poor prognostic factors, the first-line treatment is chemotherapy. If hormone receptors are present alongside poor prognostic factors, chemotherapy and hormone therapy can be used sequentially.

- the tumour is HER2-positive: the recommended first-line treatment is trastuzumab, in combination with paclitaxel or docetaxel.

- the tumour is HER2-negative: combination chemotherapies based on anthracyclines and taxanes are used. If the patient was previously treated with anthracyclines, a regimen combining a taxane with capecitabine or bevacizumab with paclitaxel is used. If this fails, vinorelbine (alone or in combination with a fluorouracil-based product) or gemcitabine are used.

4.4. Target population

In 2005[2], the incidence of breast cancer in France was estimated at approximately 49,800 cases.
The estimate of the target population is based on the following data:
- patients at the metastatic stage from the outset account for some 5%[3] to 15%[4] of cases, i.e. 2490 to 7470.
- patients at the metastatic stage after local progression account for 28%[5] of cases, i.e. 13,944.
- 85%[6] of patients are likely to undergo chemotherapy.
On the basis of these data, the number of patients with metastatic breast cancer who are able to be treated with chemotherapy is estimated at 14,000 to 18,000 patients per year.

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%

[2] Presentation of the most recent data on cancer incidence and mortality in France and the trends over the past 25 years (1980-2005) - Press conference held on 21 February 2008. INVS/Hôpitaux de Lyon/FRANCIM/INCA
[3] FRANCIM
[4] FNCLC [French Federation of Cancer Centres] survey
[5] Louis Harris survey, 2003
[6] Louis Harris survey, 2003