![HAS — HAUTE AUTORITÉ DE SANTÉ]

TRANSPARENCY COMMITTEE

OPINION

16 December 2009

JAVLOR 25 mg, solution for infusion
Pack of 1 vial of 2 ml (grey butyl elastomer stopper) – CIP: 396 428-2
Pack of 10 vials of 2 ml (grey butyl elastomer stopper) – CIP: 575 739-2
Pack of 1 vial of 4 ml (grey butyl elastomer stopper) – CIP: 396 429-9
Pack of 10 vials of 4 ml (grey butyl elastomer stopper) – CIP: 575 740-0
Pack of 1 vial of 10 ml (grey butyl elastomer stopper) – CIP: 396 430-
Pack of 10 vials of 10 ml (grey butyl elastomer stopper) – CIP: 575 741-7
Pack of 1 vial of 2 ml (black butyl elastomer stopper) – CIP: 396 431-3
Pack of 10 vials of 2 ml (black butyl elastomer stopper) – CIP: 575 742-3
Pack of 1 vials of 4 ml (black butyl elastomer stopper) – CIP: 396 433-6
Pack of 10 vials of 4 ml (black butyl elastomer stopper) – CIP: 575 744-6
Pack of 1 vial of 10 ml (black butyl elastomer stopper) – CIP: 396 434-2
Pack of 10 vials of 10 ml (black butyl elastomer stopper) – CIP: 575 745-2

Applicant: PIERRE FABRE MEDICAMENT

Vinflunine
ATC code: L01CA05

List I
Medicine for hospital prescription only. To be prescribed only by oncologists or haematologists, or doctors competent in oncology.

Date of Marketing Authorisation (centralised European): 21 September 2009

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

Medical, Economic and Public Health Assessment Division

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1. CHARACTERISTICS OF THE MEDICINAL PRODUCT

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1.1. Active ingredient
Vinflunine

1.2. Background
Vinflunine binds to tubulin at or near to vinca alkaloid-binding sites inhibiting its polymerisation into microtubules, which results in disruption of microtubule dynamics, mitotic arrest and apoptosis.

1.3. Indication
"JAVLOR is indicated in monotherapy for the treatment of adult patients with advanced or metastatic transitional cell carcinoma of the urothelial tract after failure of a prior platinum-containing regimen.
Efficacy and safety of vinflunine have not been studied in patients with Performance Status (PS) $\geq$ 2."

1.4. Dosage
"The recommended dosage is 320 mg/m² vinflunine as a 20 minute intravenous infusion every 3 weeks.
In case of WHO/ECOG performance status (PS) of 1 or of 0 with prior pelvic irradiation, the treatment should be started at the dose of 280 mg/m². In the absence of any haematological toxicity during the first cycle causing treatment delay or dose reduction, the dosage should be increased to 320 mg/m² every 3 weeks for the following cycles."

2. SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification (2009)
L   Antineoplastic and immunomodulating agents
L01   Antineoplastic agents
L01C   Plant alkaloids and other medicinal products of natural origin
L01CA   Vinca Alkaloids and analogues
L01CA05   Vinflunine

2.2. Medicines in the same therapeutic category
Comparator drugs
None

2.3. Medicines with a similar therapeutic aim
- ADRIBLASTINE (doxorubicin) and its generic drugs
- VELBE (vinblastin)
- METHOTREXATE BELLON (methotrexate)
- GEMZAR (gemcitabine)
- CISPLATYL (cisplatin).

3. ANALYSIS OF AVAILABLE DATA

The dossier contains two non-comparative phase II studies (L00070 IN 202 P1 and CA 183001) which will not be described in detail in this document and one phase III comparative study (L00070 IN 302 P1) which is analysed below.

3.1. Efficacy

Randomised (2:1), open-label, phase III Study (L00070 IN 302 P1) evaluating JAVLOR plus best supportive care (BSC) versus BSC alone in patients with advanced or metastatic transitional-cell urothelial carcinoma failing platinum-based chemotherapy.
Best supportive care allowed comprise analgesics, corticosteroids, transfusions and palliative radiotherapy.

Primary endpoint: overall survival defined as the time from randomisation to death from any cause.

Secondary endpoints[1]:
- Percentage of objective response, time to response, response duration, percentage and disease control and progression-free survival in patients treated by JAVLOR,
- Patient quality-of-life (QoL) (EORTC QLQ C30 questionnaire) and clinical benefit,
- Safety.

JAVLOR was administered at two dosages:
- 320 mg/m^2 in patients with an ECOG/WHO performance status of 0 who had not received previous pelvic radiotherapy and
- 280 mg/m^2 in patients with a ECOG/WHO status of 1 or of 0 who had received prior pelvic radiotherapy. The dosage was increased to 320 mg/m^2 in patients not presenting haematological toxicity after the first cycle.

Results:
A total of 370 patients were randomised (2:1): 253 in the JAVLOR + BSC arm and 117 in the BSC arm.
The median age of patients was 64.2 years.
Eligible patients had a performance status of from 0 to 1 (32% had a performance index of 0) and 45% had a creatinine clearance (ClCr) over 40 ml/min. Patients with severe renal impairment (ClCr less than 40 ml/min) accounted for 4% of cases.
Visceral involvement was present in 74% of patients.

The study objective was not reached in the ITT population: median overall survival was 6.9 months (95% CI [5.7 – 8.0 months]) in the JAVLOR arm versus 4.6 months (95% CI [4.1 – 7.0 months]) in the comparator arm (RR= 0.88; 95% CI [0.69 – 1.12], NS).
Two other types of analysis were also performed on overall survival. According to a multivariate analysis taking into account predefined prognostic factors (performance status, visceral involvement, alkaline phosphatases, haemoglobin and pelvic radiotherapy), the HR was 0.77 (95% CI [0.61 - 0.98], p = 0.036). In an analysis concerning the eligible population (ITT population excluding 13 patients for major protocol violations), the HR was 0.78 (95% CI [0.61 - 0.99], p = 0.040).

A partial response was observed in 16 of the 253 patients in the JAVLOR + BSC arm. The median time from randomisation to first response was 2.1 months. The median duration of response was 7.4 months in the JAVLOR + BSC arm.

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[1] See details in appendix 1

Progression-free survival was 3 months in the JAVLOR + BSC arm versus 1.5 months in the comparator arm, p = 0.0012.

During the study, 37% of patients were prescribed a morphine derivative in the JAVLOR + BSC arm versus 29% in the BSC arm.

Complementary palliative radiotherapy was administered to 23.9% of patients in the BSC arm and 4% of patients treated by JAVLOR + BSC.

There was no difference in the quality of life assessment and clinical benefit between the two arms.

3.2. Adverse effects

Treatment discontinuations for adverse reactions were reported in 23% of the patients in the JAVLOR + BSC arm versus 7% in the comparator arm.

The following haematological adverse effects were observed in the JAVLOR arm: grades 3-4 neutropenia in 50% of cases, including 6% febrile neutropenia and grades 3-4 anaemia in 20% of cases. In the comparator arm, the incidence of grades 3-4 neutropenia was 0.9% and that of grades 3-4 anaemia was 8.1%.

A higher incidence of non-haematological adverse effects was reported in the JAVLOR + BSC arm than in the BSC arm. These were: asthenia/fatigue (75% vs 61%), constipation (60% vs 25%) and nausea (51% vs 21%), peripheral sensory neuropathy (24% vs 11%).

According to the SPC "A few QT interval prolongations have been observed after the administration of vinflunine. This effect may lead to an increased risk of ventricular arrhythmias although no ventricular arrhythmias were observed with vinflunine. Nevertheless, vinflunine should be used with caution in patients with increased risk of the cardiac arrhythmia (e.g., congestive heart failure, known history of QT interval prolongation, hypokalaemia)".

3.3. Conclusion

In a randomised, open-label, phase III study, JAVLOR + BSC was compared with BSC alone in 370 patients with advanced or metastatic transitional-cell urothelial carcinoma failing platinum-based chemotherapy. Eligible patients had a performance status of from 0 to 1.

The study objective was not reached in the ITT population: median overall survival was 6.9 months (95% CI [5.7 - 8.0 months]) in the JAVLOR arm versus 4.6 months (95% CI [4.1 – 7.0 months]) in the comparator arm (RR= 0.88; 95% CI [0.69 – 1.12], NS).

Two other types of analysis were also performed on overall survival. In a multivariate analysis taking into account predefined prognostic factors (performance score, visceral involvement, alkaline phosphatases, haemoglobin and pelvic irradiation), the HR was 0.77 (95% CI [0.61 - 0.98], p = 0.036). In an analysis of the eligible population (ITT population excluding 13 patients with protocol violations), the HR was 0.78 (95% CI [0.61 - 0.99], p = 0.040).

Progression-free survival was 3 months in the JAVLOR + BSC arm versus 1.5 months in the comparator arm.

There was no major difference in the quality of life assessment between the two groups.

The main toxicities associated with JAVLOR treatment were haematological (50% grades 3-4 neutropenia and 20% of grades 3-4 thrombocytopenia) and neurological adverse effects (sensory peripheral neuropathy was observed in 24% of patients).

4. TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit

Transitional-cell urothelial carcinoma is mainly represented by bladder cancer. It is a life-threatening disease;

This proprietary drug is intended to provide curative treatment;

The efficacy/adverse effects ratio is moderate;

It is intended for second-line therapy;

There is no validated alternative medication;

Public health benefit:

>Transitional-cell urothelial carcinoma is a serious clinical condition. However, the public health burden of these carcinomas (including bladder cancer which is the most frequent malignant tumour) is low.

>Taking into account the current prognosis following the usual management of the patients concerned, there is an unmet therapeutic need for treatment in terms of public health.

>However, a review of the clinical data shows that JAVLOR is not expected to improve morbidity or mortality or the quality of life of these patients.

>Consequently, no public health benefit is expected from JAVLOR in this indication.

The actual benefit of JAVLOR is moderate.

4.2. Improvement in actual benefit

JAVLOR does not improve actual benefit (IAB V) in the management of advanced or metastatic transitional-cell urothelial carcinoma.

4.3. Therapeutic use

The reference treatment for metastatic urothelial cancers is based on chemotherapy. For the last 20 years no drug has been shown to be superior to the M-VAC combination (methotrexate, vinblastine, adriamycin and cisplatin) in terms of response rate and five-year survival. The gemcitabine-cisplatin (GC) combination gives similar results with fewer adverse effects. The improvement in the tolerability of M-VAC by using G-CSF (granulocyte/colony stimulating factor) has made it possible to propose a new dosing regimen: M-VAC-HD. Currently, M-VAC-HD and GC are the two polychemotherapies recommended for first-line treatment.

If this fails, second-line chemotherapy may be recommended, if the patient's general status permits. There is no validated standard-of-care therapy. Published series on second line treatments (paclitaxel alone[2] or in combination with gemcitabine[3], docetaxel alone[4] or in combination with ifosfamide[5], pemetrexed[6]) give response rates of less than one patient out of three and a median overall survival of from 7 to 11.5 months.

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[2] Vaughn DJ, Broome CM, Hussain M, Gutheil JC, Markowitz AB. Phase II trial of weekly paclitaxel in patients with previously treated advanced urothelial cancer. J Clin Oncol 2002;20(4):937- 40.

[3] Kanai K,· Kikuchi E, · Ohigashi T, Miyajima A, · Nakagawa K, Nakashima J, Oya M. Gemcitabine and paclitaxel chemotherapy for advanced urothelial carcinoma in patients who have received prior cisplatin-based chemotherapy. Int J Clin Oncol 2008; 13:510–14

[4] McCaffrey JA, Hilton S, Mazumdar M, Sadan S, Kelly WK, Scher HI, Bajorin DF. Phase II trial of docetaxel in patients with advanced or metastatic transitional-cell carcinoma. J Clin Oncol 1997;15(5):1853-7.

[5] Krege S, Rembrink V, Börgermann C, Otto T, Rübben H. Docetaxel and ifosfamide as second line treatment for patients with advanced or metastatic urothelial cancer after failure of platinum chemotherapy: a phase 2 study. J Urol 2001;165(1):67-71

[6] Sweeney CJ, Roth BJ, Kabbinavar FF, Vaughn DJ, Arning M, Curiel RE, Obasaju CK, Wang Y, Nicol SJ, Kaufman DS. Phase II study of pemetrexed for second-line treatment of transitional cell cancer of the urothelium. J Clin Oncol 2006;24(21):3451-7.

JAVLOR has a certain but low activity with definite toxicity and constitutes a second-line treatment for urothelial cancers with no real benefit in comparison with the molecules routinely used in this situation.

4.4. Target Population

In 2005, the incidence of bladder cancer in France was 9,679[7].

Approximately 70% of patients presented superficial tumours, which have a tendency to recur but which are generally not fatal, and 30% had invasive involvement of the bladder muscle with a high risk of death from distant metastases[8]. In addition 15% of the superficial tumours may progress to metastatic disease[9].

The failure rate of first-line therapy was 59% in studies[10]. Second-line chemotherapy may be justified in these patients, i.e. in 2,300 patients per year.

Hence the target population of JAVLOR in the indication of the marketing authorisation may be estimated to be approximately 2,300 patients.

4.5. Transparency Committee recommendations

The Transparency Committee recommends inclusion on the list of medicines reimbursed by National Insurance and on the list of medicinal products approved for use by hospitals and various public services in the indication and dosage of the MA.

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[7] InVS, HCL, Francim, INCa : Presentation of the latest French cancer incidence and mortality data and trends over the last 25 years(1980-2005) – Press conference of 21 February 2008
[8] Kaufman DS, Shipley WU, Feldman AS. Bladder cancer. Lancet 2009; 374: 239-249.
[9] Gallagher D.J., Milowsky M.I., Bajorin D.F. Advanced bladder cancer : status of first-line chemotherapy and the search for active agents in the second line setting. Cancer 2008; Vol 113 n°6 : 1284-1293.
[10] von der Maase H, Hansen SW, Roberts JT, et al. Gemcitabine and cisplatin versus methotrexate, vinblastine, doxorubicin and cisplatin in advanced or metastatic bladder cancer: results of a large, randomised multinational, multicentre phase III study. J Clin Oncol 2000; 17: 3068-307

Appendix 1

- Best overall response rate (%): confirmed best complete responses (CR) and partial responses (PR) from the date of randomisation to the end of treatment.
- Objective response rate (%): total percentage of CR and PR (calculated from the confirmed best response recorded from the date of randomisation until the end of treatment).
- Progression-free survival: calculated from the date of randomisation until the date of progression or death from any cause (according to first occurrence).
- Percentage of disease control: total percentage of CR, PR and stabilisation.
- Time to response: time to first CR or PR in patients presenting a confirmed response.
- response duration: calculated in responder patients (i.e. confirmed CR and PR) from the date when the criteria of CR or PR were met for the first time until the date of disease progression or death from any cause (according to first occurrence).
- Duration of stable disease : calculated in stable patients as the time from the date of randomisation and documentation of progression or death from any cause.
- Duration of disease control: calculated in stable patients and responders (confirmed CR and PR) as the time between the date of randomisation and documentation of disease progression or death for any cause.

Response duration, duration of stabile disease and duration of disease control were censored at the time of the institution of any new treatment.

Quality of life: The health related QOL scale is the main QOL parameter in the EORTC questionnaire (QLQ-C30). Secondary QOL parameters included the 14 other scales: the 5 functioning scales and the 9 "symptom" scales.
- Response in terms of clinical benefit: the main criterion of clinical benefit was defined as an improvement during the first three months after the first dose of study medication or first visit, compared to baseline, of at least one of the following parameters, performance score, body weight, current pain severity with no prior or concomitant deterioration in another parameter (deterioration confirmed once at least three weeks later).