HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

Opinion

3 April 2013

XALKORI 200 mg, hard capsule

B/60 hard capsules (CIP: 34009 267 625 6 8)
Vial of 60 hard capsules (CIP: 34009 267 626 2 9)

XALKORI 250 mg, hard capsule

B/60 hard capsules (CIP: 34009 267 627 9 7)
Vial of 60 hard capsules (CIP: 34009 267 628 5 8)

Applicant: PFIZER

INN	crizotinib
ATC Code (2012)	L01XE16 (tyrosine kinase inhibitors)
Reason for request	**Inclusion**
Lists concerned	**National Health Insurance** (French Social Security Code L.162-17) **Hospital use** (French Public Health Code L.5123-2)
Indication concerned	**"XALKORI is indicated for the treatment of adults with previously treated anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC)."**

Actual Benefit (AB)	The actual benefit is substantial in the second-line treatment of ALK+ advanced non-small cell lung cancer (NSCLC).
Improvement in Actual Benefit	XALKORI provides a moderate improvement in actual benefit (level III) in the treatment strategy of ALK+ advanced non-small cell lung cancer as a second-line therapy and compared with docetaxel or pemetrexed.
Therapeutic use	XALKORI, a tyrosine kinase inhibitor, is the first medicinal product targeting the ALK+ mutation (4.6% of patients) with Marketing Authorisation for NSCLC. It is a second-line treatment for ALK+ advanced non-small cell lung cancer.
Committee recommendations	The Committee recommends inclusion on the list of medicines refundable by National Health Insurance and/or on the list of medicines approved for hospital use in the second-line treatment of ALK+ advanced non-small cell lung cancer.

01 ADMINISTRATIVE AND REGULATORY INFORMATION

Marketing Authorisation (centralised procedure)	23/10/2012 Conditional Marketing Authorisation: • on submission of the results from a comparative study versus standard chemotherapy (pemetrexed or docetaxel) in the indication (study 1007). • on the submission of updated safety and efficacy data from studies 1001 and 1005. • on submission of a safety review of the main serious hepatic disorders reported in the main studies. Risk Management Plan (RMP) in particular including monitoring of the following risks: Significant effects: - monitoring of major effects from clinical studies: - hepatotoxicity, - interstitial pneumonitis, - visual disorders, - bradycardia - QT interval prolongation Potentially significant effects: Potential risks: renal cysts, oedema, leukopenia, photosensitivity, neuropathy, troubles with reproduction. Missing Information: - patients with hepatic impairment - patients with renal impairment - elderly population - paediatric population - Women who are pregnant, breastfeeding or are of childbearing potential - CYP3A inhibitors/inducers and glycoprotein p substrates, proton pump inhibitors and H2 inhibitors - patients undergoing long-term treatment
Prescribing and dispensing conditions / special status	List I Medicine for hospital prescription only, restricted to oncologists or doctors with cancer training. Medicine requiring monitoring during treatment. In France, crizotinib was made available under a temporary authorisation for use by a named patient (ATU nominative) from 18 November 2010 and under temporary authorisation for use by a cohort (ATU de cohorte) from 2 April 2012. On 12 April 2012, 116 temporary authorisations for use by a named patient and 14 temporary authorisations for use by a cohort were awarded in the same indication.

ATC Classification	2012	
	L	Antineoplastic and immunomodulating agents
	L01	Antineoplastic agents
	L01X	Other antineoplastic agents
	L01XE	Protein kinase inhibitors
	L01XE16	crizotinib

02 BACKGROUND

This is a request for the inclusion of XALKORI, the first tyrosine kinase inhibitor targeting the ALK+ mutation in lung cancer.

03 THERAPEUTIC INDICATION

"XALKORI is indicated for the treatment of adults with previously treated anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC)."

04 DOSAGE

"Treatment with crizotinib should be initiated and supervised by a physician experienced in the use of anticancer medicinal products.

ALK Testing
An accurate and validated ALK assay is necessary for the selection of patients for treatment with XALKORI.

Dosage
The recommended initial dose schedule of XALKORI is 250 mg orally, twice daily, taken continuously.
Treatment should be continued as long as the risk benefit ratio remains favourable."

05 THERAPEUTIC NEED

The therapeutic management of non-small cell lung cancer (NSCLC) is different depending on the stage of the disease. For early stages, the reference treatment is surgery. However, early stages only represent approximately 25% to 30% of these cancers, as a large proportion are diagnosed at an advanced stage (25% to 30% at locally advanced stage and 40% at metastatic stage).
For advanced stages, the treatment is medical. Second-line treatments available for NSCLC are cytotoxic agents (ALIMTA (pemetrexed), TAXOTERE (docetaxel) and TARCEVA (erlotinib), all of which do not have a specific action on the ALK+ mutation.
Crizotinib, a tyrosine kinase inhibitor, is the first medicinal product targeting the ALK+ mutation with a Marketing Authorisation for NSCLC. This ALK+ mutation is found in 4.6% of patients with advanced stage lung cancer.[1] [2]

Determination of ALK translocation
The diagnostic examination for XALKORI (crizotinib), which determines if the ALK translocation is present or not from a sample rich in cancer cells, is financially reimbursed by the French Healthcare System and is performed at cancer molecular genetics hospital platforms (plateformes hospitalières de génétique moléculaire des cancers) financed by the French National Cancer Institute (INCa) and the Directorate-General for Healthcare Provision (DGOS). These platforms are found across the whole of the country. There is one in most regions in France and: "their aim is to perform innovative molecular tests for all patients in the region regardless of the establishment in which they are being treated." The need represented by this examination, which is a prerequisite

[1] Shaw AT, Yeap BY, et al. Clinical features and outcome of patients with non-small-cell lung cancer Who Harbor EML4-ALK. Journal of Clinical Oncology 2009; 27:4247-4253
[2] Rodig SJ, Mino-Kenudson M, Dacic S et al. Unique clinicopathologic features characterize ALK-rearranged lung adenocarcinoma in the western population. Clin Cancer Res. 2009 15(16):5216-23

for using XALKORI (crizotinib), is therefore covered by these platforms, with an equal opportunity to receive it for all patients. It is not the method included on the List of procedures and services defined in Article L. 162-1-7 of the French Social Security Code (i.e. the nomenclature of procedures reimbursed by National Health Insurance), that ensures its funding. Nevertheless, inclusion of this examination on the List of procedures and services is possible, but it will require assessment by HAS.

06 CLINICALLY RELEVANT COMPARATORS

06.1 Medicinal products

Second-line treatments for non-small cell lung cancer are represented by cytotoxic agents that do not have a specific action on the ALK+ mutation and are listed below:

- ALIMTA (pemetrexed) is indicated as monotherapy for the second-line treatment of patients with locally advanced or metastatic non-small cell lung cancer other than predominantly squamous cell histology.
- TAXOTERE (docetaxel) is indicated for the treatment of patients with locally advanced or metastatic non-small cell lung cancer after failure of prior chemotherapy.
- TARCEVA (erlotinib), targeted therapy, is indicated for the treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) after failure of at least one chemotherapy regimen.

When prescribing TARCEVA, factors associated with prolonged survival should be taken into account. No survival benefit or other clinically relevant effects of the treatment have been demonstrated in patients with Epidermal Growth Factor Receptor (EGFR) negative tumours.

Conclusion

There are no relevant comparator medicines available with a specific Marketing Authorisation for the treatment of lung cancer with the ALK+ mutation.

07 INTERNATIONAL INFORMATION ON THE MEDICINAL PRODUCT

Country	Reimbursement		
	Date reimbursement started	Yes/No/Assessment in progress	Scope (indications) and condition(s)
USA	26 August 2011	yes	First line ALK-positive locally advanced or metastatic non-small cell lung cancer
Germany	15 November 2012	yes	Second line ALK-positive locally advanced or metastatic non-small cell lung cancer
Austria	December 2012	yes	Idem
Denmark	26 November 2012	yes	Idem
Rest of Europe	Still being assessed		

08 ANALYSIS OF AVAILABLE DATA

The submitted dossier comprises of:
- study 1001 – a phase I/II study
- study 1005 – a phase II study
- a phase III comparative study (study 1007) versus standard chemotherapy with docetaxel or pemetrexed.

08.1 Efficacy

Study 1001
Study 1001 was originally designed as a phase I escalating dose study on patients presenting with any type of ALK+ tumour (with the exception of leukaemia), to determine the maximum safe dose for phase II. The efficacy of crizotinib was observed in two patients who presented with ALK+ NSCLC treated during the escalating dose period; it was decided to recruit more ALK+ NSCLC patients. The results below are only for previously treated ALK+ NSCLC patients.

The amended aims for this study therefore became:
- the objective response rate according to therapeutic response in solid tumours (RECIST[3]) evaluation criteria
- overall survival
- duration of response to treatment
- the disease control rate after 8 and 16 weeks of treatment
- progression-free survival
- safety

Results
Patients included had a median age of 51 years and were predominately non-smokers. Half of the patients included in the study were male.
Most patients had an ECOG performance index evaluated at 0 or 1 (87.2%) and 13% of patients had an index of 2-3 at the start of treatment.
The cancers were primarily of an adenocarcinoma type histology (98%).

Table 1: Efficacy results for study 1001 in ALK-positive advanced NSCLC

Efficacy endpoints	Study 1001 (n = 121)
Overall response (FR + PR),[a] n (%) [95% CI]	73 (60.3) [51.0, 69.1]
Median delay in tumour response, weeks [95% CI]	7.9 (2.6 – 39.6)
Median duration of response, weeks [95% CI][c]	48.1 [35.7, 64.1]
Progression-free survival, median	9.2 months [7.3 months, 12.7 months]
Overall survival, median	Not achieved
Overall survival (OS), probability of survival at 12 months[b] [% (95% CI)]	72% (63%, 80%)

[3] Corresponds to criteria used to evaluate the response in solid tumours and is summarised as follows:
- Full response: disappearance of all tumour lesions
- Partial response: reduction of 30% in the largest lesion diameter
- Disease progression: increase of 20% in the largest lesion diameter
- Stable disease: changes in tumour size not meeting the conditions indicated previously.

[a] The response was not evaluated in four patients
[b] The duration of treatment was evaluated by Kaplan Meier analysis

The objective response rate was 60.3% (95% CI: 51-69.1).
The median time to achieve a response was 7.9 weeks (95% CI: 2.1-39.6).
The median treatment duration was estimated as 48.1 weeks (95% CI: 35.7-64.1).
The median progression-free survival was 9.2 months (95% CI: [7.3-12.7]).
At the time of the analysis, 60 patients (48%) had seen progression in their disease and 14 patients (11.2%) had died; the median overall survival could not be evaluated.

Study 1005
A non-comparative phase II study that evaluated the efficacy and safety of crizotinib 250 mg taken orally, twice daily and continuously, in patients with ALK+ advanced non-small cell lung cancer and with at least one failed chemotherapy regimen.

The primary efficacy endpoint was the objective response rate according to therapeutic response in solid tumours (RECIST criteria) evaluation criteria.

Secondary endpoints were:
- delay in tumour response
- duration of response
- disease control rate
- progression-free survival
- overall survival.

Results:

Analysis of efficacy was based on 255 patients.
Patients included had a median age of 52 years, and were predominately non-smokers. Nearly half (45%) of patients included were male.
The majority of patients had an ECOG performance index evaluated at 0 or 1 (82%) and 18% of patients had an index of 2-3 at the start of treatment.
The cancers were primarily of an adenocarcinoma type histology (93%).
Approximately half of the patients had already received radiotherapy and the majority had undergone a surgical procedure (96%).
Only 10% of patients had received a single previous line of treatment and over half had already received at least three lines of treatments.

Table 2: Efficacy results for study 1005 in ALK-positive advanced NSCLC

Efficacy endpoint	Study 1005 (n = 255)
Objective response rate [a] [% (95% CI)]	53% (47%, 60%)
Delay in tumour response (TTR) [median (limits)]	6.1 weeks (4.9 weeks, 30.4 weeks)
Duration of response (DR) [b] [median (95% CI)]	42.9 weeks (36.1 weeks, 49.7 weeks)
Disease control rate (DCR)[c] at 6 weeks [% (95% CI)]	85% (80%, 89%)
Progression-free survival [median (95% CI)]	8.5 months (6.5 months, 9.9 months)
Median overall survival (OS)	Not achieved
Overall survival (OS), probability of survival at 12 months[b] [% (95% CI)]	61% (49%, 71%)

[a] The response was not evaluated in 6 patients.
[b] Estimated by Kaplan-Meier method.
[c] Proportion of patients presenting with full response, a partial response or a stable disease at 6 weeks, defined according to RECIST criteria.

The objective response rate was 53.3% according to study investigators and 50.8% according to the independent review board. Four (1.6%) had a full response, 132 (51.8%) a partial response and 80 (31.4%) had stabilisation of their disease for at least 6 weeks.
The median delay in achieving a response was 6.1 weeks.
The median treatment duration was 42.9 weeks.
The median progression-free survival was 8.5 months.
Of the 136 patients who responded to treatment, 35 (25.7%) had progression in their disease or died.
The median overall survival was not achieved at the time of the analysis.

Study 1007

A randomised, open-label study that compared crizotinib (XALKORI) with standard chemotherapy treatment (pemetrexed or docetaxel) in patients with ALK+ advanced non-small cell lung cancer and with one failed chemotherapy regimen.

The primary efficacy endpoint was progression-free survival, defined as the time from randomisation to documentation of disease progression, or death from any cause. Blind reading of x-rays was performed by an independent committee.

The secondary endpoints were:

- objective response rate
- overall survival
- quality of life

Treatment and randomisation:
Randomisation was performed to assign patients into the crizotinib or chemotherapy treatment groups, according to a 1:1 ratio, stratified on the following parameters:

- ECOG criterion (0-1, 2)
- presence of cerebral metastases
- previous treatment with a tyrosine kinase inhibitor targeting the EGFR

Patients received:

- in the crizotinib group - 250 mg twice daily, orally, taken continuously
- in the chemotherapy group with 21 day cycles:
  - pemetrexed 500 mg/m^2 on Day 1 of each cycle
    or
  - docetaxel 75 mg/m^2 on Day 1 of each cycle

The first choice for patients randomised into the chemotherapy group was pemetrexed, except if the patient had already received it or presented with squamous cell histology.[4]
Each of these treatments was continued until disease progression, death, toxicity judged as unacceptable or withdrawal of consent.

Inclusion criteria:

- patients aged over 18 years with ALK+ NSCLC,*

*Patients should present with either translocation or inversion of ALK gene, confirmed using FISH (fluorescent in situ hybridation) with signal separation. Investigation of the ALK genome abnormality was performed by a central laboratory.

- Measurable tumour according to RECIST criteria,
- ECOG status between 0 and 2,
- Patients with progression after previous platinum-based chemotherapy.

[4] Pemetrexed does not have Marketing Authorisation in this histology group

Non-inclusion criteria:

- patients who received previous therapy targeting ALK;
- previous treatment with crizotinib;
- squamous cell histology for the patients randomised in the pemetrexed group
- grade 2 or higher peripheral neuropathy for the patients randomised into group B, on docetaxel;
- hypersensitivity reaction to medicinal products containing polysorbate 80 for the patients randomly affected in group B, on docetaxel;
- persistent grade 2 cardiac arrhythmia according to the National Cancer Institute (NCI CTCAE) classification; uncontrolled atrial fibrillation (any grade), or a QTc interval greater than 470 msec;
- pregnant or breastfeeding;
- history of cancer (other than current NSCLC);
- presence of interstitial fibrosis or interstitial lung disease.

Statistical method

The intention to treat (ITT) population was made up of all randomised patients.
The per protocol (PP) population was made up of all patients randomised who received the treatment they were assigned on randomisation at least once.
The assessable population for quality of life was made up of all randomised patients who had a quality of life assessment on entry and during treatment.
Analyses for efficacy were carried out on the ITT population.
The efficacy endpoints (progression-free survival “PFS” and overall survival “OS”) were analysed using the Kaplan-Meier method, with a unilateral log-rank test.
The objective response rates were compared using a Pearson test and a Cochrane Mantel Haenszel test, adjusted for the stratification variants.
An interim analysis was not scheduled for PFS. The final analysis was carried out when 217 events had occurred (disease progression or death).
An interim analysis of overall survival was scheduled at the time of the analysis of PFS. The final analysis of overall survival will take place when 241 deaths have occurred.
To control the inflation in alpha risk as the result of repetition of statistical tests, a test procedure was used with gradual reduction in risk in the following order: PFS, ORR and OS. PFS and ORR were tested using a unilateral method with a significance threshold equal to 0.025 (bilateral test equivalent to 0.05). The overall survival was tested using a unilateral method with a level equal to 0.0004, corresponding to the number of events observed at the end of the PFS analysis.

Results:

A total of 347 patients were included. The median age was 51 years in the crizotinib group and 49 years in the chemotherapy group. More than half of patients in each group had an ECOG performance index evaluated at 1 or 2 at the start of treatment.
The cancers were mainly of an adenocarcinoma type histology in the two treatment groups (94.2% for the crizotinib group and 92% for the chemotherapy group) and 35% of patients had cerebral metastases.

Table 3: Baseline patient characteristics

	Crizotinib N=173	Chemotherapies N=174
Gender (n (%)) Male Female	 75 (43) 98 (57)	 78 (45) 96 (55)
Age (years) Median Minimum, Maximum	 51 22, 81	 49 24, 85
ECOG performance index n (%) 0 1 2	 72 (41.6) 84 (48.6) 16 (9.2)	 65 (37.4) 95 (54.6) 14 (8.0)
Smoking status n (%) Non-smoker Previous smoker Current smoker	 108 (62.4) 59 (34.1) 5 (2.9)	 111 (63.8) 54 (31.0) 9 (5.2)
Histological classification Adenocarcinoma Large cell carcinoma Squamous cell carcinoma Adenosquamous carcinoma Other	 164 (94.2) 1 (<1.0) 0 4 (2.3) 4 (2.3)	 160 (92.0) 3 (1.7) 1 (<1.0) 3 (1.7) 7 (4)
Presence of cerebral metastases Yes No	 60 (34.7) 113 (65.3)	 60 (34.5) 114 (65.5)
Previous treatment received with tyrosine kinase inhibitors targeting EGFR: Yes No	 20 (11.6) 153 (88.4)	 21 (12.1) 153 (87.9)

Results for the primary efficacy endpoint

On 30 March 2012, the independent review board documented 227 patients who progressed or died under treatment (100/173 (57%) patients in the crizotinib group and 127/174 (73%) in the chemotherapy group).
The median progression-free survival was 7.7 months in the crizotinib group versus 3.0 months in the chemotherapy group, which is an absolute difference of 4.7 months in favour of the crizotinib group (HR = 0.49 95% CI: [0.37 - 0.64]; p <0.0001).

Sub-group analysis:
Among the 174 patients randomised into the standard chemotherapy group, 72 of the 99 (73%) patients who received pemetrexed progressed or died and 54 of the 72 (75%) patients who received docetaxel progressed or died.
The median progression-free survival was 7.7 months in the crizotinib group versus 4.2 months in the pemetrexed sub-group and 2.6 months in the docetaxel sub-group.

Results for the secondary efficacy endpoints

- objective response
The objective response rate was higher in the crizotinib group (65.3%) than in the chemotherapy group (19.5%). The hazard ratio (crizotinib:chemotherapy) was 3.4 (95% CI: 2.5 – 4.7) with a p<0.0001. A hazard ratio greater than 1 indicates a higher probability of response in the crizotinib group.

The objective response rate in the pemetrexed sub-group was 29.3% (95% CI: 21%, 39%) (p<0.0001 vs. crizotinib) and 6.9% in the docetaxel sub-group (95% CI: 2%, 16%) (p<0.0001 vs. crizotinib).

- overall survival
During the analysis of the primary efficacy endpoint of the study, no difference in terms of overall survival between the crizotinib group and the chemotherapy group was observed (96 deaths observed: 28% in the crizotinib group versus 27% in the chemotherapy group.) The HR was 1.02, 95% CI: [0.68 - 1.54]; p =0.539.
This analysis corresponds to an interim analysis of overall survival (241 deaths were required for the final analysis).
At the time of the analysis, 49% of patients in the crizotinib group were still on treatment versus 16% in the chemotherapy group (patients who progressed were able to receive crizotinib in study 1005).

- quality of life
The quality of life assessment results were heterogeneous: improvements in certain aspects, such as fatigue, dyspnoea, insomnia and chest pain on XALKORI in comparison with chemotherapy while other aspects assessed, such as diarrhoea and constipation showed deterioration with XALKORI.
As this was an open-label study, the results from this analysis should be interpreted with caution.

08.2 Adverse effects

a/ Safety data taken from the comparative study:
The frequency of treatment discontinuation due to an adverse event was 17% in the crizotinib group and 14% in the chemotherapy group.
The main grade 3 or 4 adverse events were: elevation in transaminases (15.7% in the crizotinib group versus 2.3% in the chemotherapy group), pulmonary embolism (5.2% vs. 1.7% in the chemotherapy group) and neutropenia (13.3% versus 19.2% in the chemotherapy group).

b/ Safety data from the non-comparative studies (1001 and 1005):
The incidence of treatment discontinuation for adverse events was 12.8% in study 1001 and 12.1% in study 1005.
In study 1001, the incidence of grade 3-4 adverse events was 51.7% and that of grade 5 was 15.4%.
In study 1005, the incidence of grade 3-4 adverse events was 34.6% and that of grade 5 was 11.6%.
The main toxicities were haematological (neutropenia) or hepatological (increase in alanine aminotransferase).

08.3 Summary & discussion

XALKORI (crizotinib) obtained a conditional Marketing Authorisation in the treatment of ALK+ advanced non-small cell lung cancer on the basis of two non-comparative studies (one phase I/II study [study 1001] and one phase II study [study 1005]).
The median age of patients was 51 years in one study and 52 years in the other.
The cancers were mainly of an adenocarcinoma type histology (93% to 98% depending on the study).
The objective response rate (full[5] or partial[6] response) was 53.3% in study 1001 and 60.3% in study 1005. The median overall survival was not achieved in either of the two studies.

The Marketing Authorisation was on the condition of carrying out a comparative study versus systemic chemotherapy used in this stage of the disease.
The applicant has submitted the results from a phase III comparative study (study 1007) versus standard chemotherapy with docetaxel or pemetrexed.
This was an open-label, randomised study with the primary efficacy endpoint being progression-free survival, defined as the time from randomisation to documentation of disease progression, or death from any cause.
Objective response rate and overall survival were secondary criteria.
A total of 347 patients were included, with a median age of 51 years in the crizotinib group and 49 years in the chemotherapy group. The tumours were mainly of an adenocarcinoma type histology.
Crizotinib was superior to chemotherapy in:

- median progression-free survival (primary endpoint): 7.7 months versus 3.0 months, which is an absolute difference of 4.7 months in favour of the crizotinib group (HR = 0.49, 95% CI: [0.37 - 0.64]; p <0.0001).
- objective response rate: 65.3% versus 19.5%.

However, there was no difference in the overall survival between crizotinib and chemotherapy: 28% versus 27%; HR was 1.02, 95% CI: [0.68 - 1.54]; p =0.539.
The main grade 3 or 4 adverse events more common in the crizotinib group than in the chemotherapy group were: elevation of transaminases (15.7% versus 2.3%), pulmonary embolism (5.2% vs. 1.7%) and neutropenia (13.3% versus 19.2%).

[5] disappearance of all tumoral lesions
[6] reduction of 30% in the largest lesion diameter

09 THERAPEUTIC USE

The therapeutic management of non-small cell lung cancer differs depending on the stage of the disease.
The reference treatment for early stage non-small cell lung cancer is surgery. However, a large proportion of patients are diagnosed at an advanced stage of the disease (about 25% to 30% in the locally advanced stage and 40% in the metastatic stage) and the early stage accounts for only about 25 to 30%.
The management of these cancers is through systemic treatment. The treatment strategy is guided based on whether there is the presence of a mutation of the EGFR gene or not. Other criteria are also used when making a treatment decision: histology of the tumour, the performance score of the patient and their comorbidities.
As a first-line therapy, the reference treatment is a dual therapy combining a third generation molecule with cisplatin or carboplatin in cases where cisplatin is contraindicated.
To date, the third generation molecules that have shown a benefit as a first-line treatment are: gemcitabine, taxanes (docetaxel and paclitaxel), vinorelbine and pemetrexed. Tyrosine kinase inhibitors are not indicated in these patients.
In cases of non-squamous cell predominant tumours, bevacizumab can also be added to the combination of a third generation molecule and a platinum salt.
As a second-line therapy, the reference treatment is monotherapy chemotherapy with a third generation chemotherapy agent (pemetrexed only for non-squamous cell predominant tumours or docetaxel), or a targeted therapy (erlotinib or gefitinib, if this has not been administered as a first-line treatment). However, no survival benefit or other clinically relevant effects of the treatment have been demonstrated in patients with Epidermal Growth Factor Receptor (EGFR) negative tumours. These treatments are maintained until progression of the disease occurs.
ALK+ NSCLC is a recently identified molecular sub-entity of NSCLC (Soda et al, 2007).[7] Therefore, treatments currently available for patients with ALK+ NSCLC are treatments usually given for NSCLC without taking into consideration the genome abnormality and there are no specific guidelines for this sub-group of patients.

XALKORI, a tyrosine kinase inhibitor, is the first medicinal product targeting the ALK+ mutation (4.6% of patients) with Marketing Authorisation for NSCLC. It is a second-line treatment for ALK+ advanced non-small cell lung cancer.

[7] Soda M, Choi YL, et al. Identification of the transforming EML4-ALK fusion gene in non-small-cell lung cancer. Nature Publishing Group 2007; 448: 561-566

010 TRANSPARENCY COMMITTEE CONCLUSIONS

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

010.1 Actual benefit

◗ Non-small cell lung cancer (NSCLC) is a serious and life-threatening condition;
◗ This medicinal product is intended as a curative therapy, specifically for NSCLC;
◗ The efficacy/adverse effects ratio is high;

◗Public health benefit:

In France, lung cancer is the number one cause of mortality in men, number three in women, and is a major public health burden. The burden of locally advanced or metastatic non-small cell lung cancer (NSCLC) (80 to 85% of lung cancers) is itself substantial. The burden represented by the population likely to benefit from XALKORI (patients with anaplastic lymphoma kinase (ALK)-positive and advanced NSCLC (<5% of patients)), as a second-line therapy, may be considered as low due to the very small number of patients concerned.
Improving the management of cancer patients and their quality of life is a public health need which is an established priority (French Public Health Law of 2004, the Cancer Plan and the plan for improving the quality of life of patients with chronic diseases).
In view of the available clinical data, in particular a study versus chemotherapy with docetaxel or pemetrexed showing an absolute increase of 4.7 months in progression-free survival in favour of XALKORI, with a significant improvement in objective response rate as well as quality of life, a moderate additional impact in terms of morbidity, mortality and quality of life is expected in patients treated with XALKORI as a second-line therapy compared with chemotherapy. It should be noted that there was no difference observed in terms of overall survival.
The transferability of the results of the studies to clinical practice is considered as acceptable.
However, in the same way as oral chemotherapies, XALKORI is likely to have an impact on the organisation of the healthcare system (stays in hospital avoided, transfer of management to consultations), which was not documented.
Consequently, from a population point of view, it is not expected that the proprietary medicinal product XALKORI will benefit public heath in this indication.

◗ Standard chemotherapy is an alternative medicinal product; however it does not target the ALK+ mutation;
◗ This product is a second-line therapy;

Taking account of these points, the Committee considers that the actual benefit of XALKORI is substantial in the second-line treatment of anaplastic lymphoma kinase (ALK) positive advanced non-small cell lung cancer (NSCLC).

010.2 Improvement in actual benefit (IAB)

XALKORI provides a moderate improvement in actual benefit (level III) in the treatment strategy of ALK+ advanced non-small cell lung cancer as a second-line therapy and compared with docetaxel or pemetrexed.

010.3 Target population

Patients eligible for treatment with XALKORI are adult patients who were previously treated with chemotherapy for anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC).

The incident target population of XALKORI in non-squamous cell ALK-positive NSCLC can be estimated based on the following data:
According to 2011 projections, in France, lung cancer has approximately 39,500 new cases per year.
Non-small cell lung cancer represents 85% of all lung cancers, which is 33,575 cases per year.
Approximately 65% of patients are diagnosed at an advanced or a metastatic stage of the disease (stage IIIb- IV), which is 21,824 cases.
Approximately 35% of patients are diagnosed at a localised or locally advanced stage (stage I-IIIa); among these patients, 40% will develop an advanced or metastatic stage, which is 4,701 cases.
Consequently, the population eligible for first-line treatment for NSCLC is estimated at approximately 26,525 patients.
Approximately 65% of NSCLC are of the non-squamous cell sub-type, which is 17,241 cases.
Among these, approximately 4.6% are ALK-positive, which is 793 patients.
Approximately 80% of patients with non-squamous cell ALK-positive NSCLC will receive a second-line treatment after failure of a previous treatment, which is approximately 630 patients.

The target population of XALKORI in previously treated, non-squamous cell ALK-positive advanced NSCLC is estimated at approximately 630 patients per year.

In summary, the target population of XALKORI is estimated at approximately 630 patients per year.

011 TRANSPARENCY COMMITTEE RECOMMENDATIONS

The Committee recommends inclusion on the list of medicines refundable by National Health Insurance and/or on the list of medicines approved for hospital use in the second-line treatment of ALK+ advanced non-small cell lung cancer.

◗Packaging

Appropriate for the prescription conditions according to the indication, the dosage and the treatment duration.

◗Proposed reimbursement rate: 100%