HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

Opinion
29 October 2014

PROLEUKIN 18 million IU

Pack of 1 vial of powder for solution for injection (CIP CODE: 34009 562 158 6 7)
Pack of 1 vial of powder for solution for infusion (CIP CODE: 34009 562 155 7 7)

Applicant: NOVARTIS

INN	Aldesleukin
ATC code (year)	L03AC01 (interleukin)
Reason for the review	**Re-assessment of the IAB following joint referral from the Ministry of Health, the Social Security Directorate and the Directorate General for Health Services on 10 October 2013 and in accordance with article R 163-19 of the French Social Security Code.**
List concerned	**Hospital use** (French Public Health Code L.5123 2)
Indication concerned	**"Treatment of metastatic renal cell carcinoma.** **Risk factors associated with decreased response rates and median survival are:** **· of ECOG* or greater** **· More than one organ with metastatic disease sites,** **· A period of < 24 months between initial diagnosis of primary tumour and the date the patient is evaluated for PROLEUKIN treatment.** **(*) ECOG (Eastern Cooperative Oncology Group) performance status: 0 = normal activity; 1 = symptoms but ambulatory; 2 = in bed less than 50% of time; 3 = in bed more than 50% of time, limited self-care; 4 = completely disabled, no self-care.** **Response rates and median survival decrease with the number of risk factors present. Patients positive for all three risk factors should not be treated with PROLEUKIN."**

Actual Benefit	**Low actual benefit**
IAB	**In view of:** - **limited available data (old, uncontrolled studies)** - **the absence of specific data in the current Marketing Authorisation population and for the validated dosages,** **but considering that PROLEUKIN may have a (marginal) role in the therapeutic strategy,** **the Committee estimates that these proprietary medicinal products do not provide any improvement in actual benefit (level V, non-existent) in the current management of patients with metastatic renal cell carcinoma.**
Therapeutic use	**Since the arrival of so-called targeted therapies, the role of PROLEUKIN has been marginalised in the therapeutic strategy; it is limited to a selected subset of patients with a good prognosis as defined by the French immunotherapy group: patients in good general health (Karnofsky index > 80%) and with a single metastatic site (usually pulmonary), in first-line treatment.**

01 ADMINISTRATIVE AND REGULATORY INFORMATION

Marketing Authorisation (procedure)	Date initiated (consultation procedure): 15/09/1989 06/02/1998: subcutaneous route (mutual recognition procedure) 28/02/1992: restriction of the wording of the indication.
Prescribing and dispensing conditions/special status	List I Hospital prescription restricted to oncology or haematology specialists or doctors with cancer training. Medicine requiring special monitoring during treatment.

ATC Classification	2013	
	L:	Antineoplastic and immunomodulating agents
	L03:	Immunostimulants
	L03A:	Cytokines and immunomodulating agents
	L03AC:	Interleukins
	L03AC01:	aldesleukin

02 BACKGROUND

As part of the work aimed at updating the list of chargeable medicinal products in addition to hospital services by the Ministerial financial advisory board for hospitalisation, and pursuant to article R 163-19 of the French Social Security Code, the Ministry of Health, the Social Security Directorate and the Directorate General for the organisation of care have applied to HAS for a ruling on the improvement in actual benefit (IAB) of proprietary medicinal products, including **PROLEUKIN 18 million IU, powder for solution for injection and powder for solution for infusion,** subject of this opinion.
Due to the length of inclusion, the IAB had not been assessed by the Committee.

The proprietary medicinal product PROLEUKIN 18 million IU was included on the list of medicines approved for hospital use and various public services by order dated 06/12/1994 published in the Official Gazette dated 17 December 1994 for the pack size of 7 10 ml vials (and Official Gazette dated 24 February 1999 for the single-dose vial pack size). By the order of 4 April 2005, published in the Official Gazette of 10 May 2005, this proprietary medicinal product was included on the list of chargeable medicinal products in addition to hospital services.

The active substance of PROLEUKIN is aldesleukin, a recombinant human interleukin-2, which has a regulatory effect on the immune response. The exact mechanism by which aldesleukin-mediated immunostimulation leads to antitumour activity is unknown.

03 THERAPEUTIC INDICATION

"Treatment of metastatic renal cell carcinoma.
Risk factors associated with decreased response rates and median survival are:

- A performance of EGOC*, 1 or greater
- More than one organ with metastatic disease sites,
- A period of < 24 months between initial diagnosis of primary tumour and the date the patient is evaluated for PROLEUKIN treatment.

*) ECOG (Eastern Cooperative Oncology Group) performance status:
0 = normal activity;
1 = symptoms but is ambulatory;
2 = in bed less than 50% of time;
3 = in bed more than 50% of time, limited self-care;
4 = completely disabled, no self care.

Response rates and median survival decrease with the number of risk factors present. Patients positive for all three risk factors should not be treated with PROLEUKIN."

For information, in the United States and Canada, PROLEUKIN also has Marketing Authorisation in the treatment of metastatic melanoma.

04 CONTRAINDICATIONS

PROLEUKIN treatment is contraindicated in the following situations:

1. Hypersensitivity to the active substance or to any of the excipients listed in section 6.1 of the SPC,
2. An ECOG performance status greater than or equal to 2*,
3. Simultaneous presence of a performance status of ECOG 1 or greater* and more than one organ with metastatic disease sites and a period of < 24 months between initial diagnosis of the primary tumour and the date the patient is evaluated for PROLEUKIN treatment.
4. A significant history or the existence of severe cardiac disease. In questionable cases a stress test should be performed,
5. Signs of active infection requiring antibiotic therapy,
6. PaO_2 < 60 mm Hg during rest,
7. Existence of severe major organ dysfunction,
8. Brain metastases or seizure disorders, with the exception of successfully treated brain metastases (normal CAT; neurologically stable status).

In addition, it is recommended to not use PROLEUKIN in the following situations:

1. White Blood Count (WBC) < 4000/mm^3; platelets < 100,000/mm^3; haematocrit (HCT) < 30%,
2. Serum bilirubin and creatinine levels outside the normal range,
3. History of organ allograft,
4. Patients who are likely to require corticosteroid therapy,
5. Pre-existing auto-immune disease.

(*) See section 4.1 of the SPC for the ECOG score.

05 DOSAGE

Three administration regimens for PROLEUKIN were studied (continuous intravenous, intravenous bolus and subcutaneous). In France, the intravenous bolus regimen is no longer authorised by the current Marketing Authorisation due to its higher toxicity.
The two modes of administration are currently validated by the Marketing Authorisation are as follows:

"PROLEUKIN should be administered intravenously by continuous infusion or by subcutaneous injection.
The following dosing regimen is recommended to treat adult patients with metastatic renal cell carcinoma:

Continuous intravenous infusion
18×10^6 IU per m^2 is administered as a continuous infusion over 24 hours for 5 days, followed by 2-6 days without PROLEUKIN therapy, an additional 5 days of intravenous PROLEUKIN therapy as a continuous infusion and 3 weeks without PROLEUKIN therapy. This constitutes one induction cycle. After the 3 weeks without PROLEUKIN therapy period of the first cycle, a second induction cycle should be given.
Maintenance: Up to four maintenance cycles (18×10^6 IU per m^2 as continuous infusion for 5 days) may be given with 4-week intervals to patients who respond or have disease stabilisation.

Subcutaneous injection
18×10^6 IU as subcutaneous (sc) injection is administered every day for 5 days, followed by 2 days without PROLEUKIN therapy. For the following 3 weeks, 18×10^6 IU sc is administered on the days 1 and 2 of each week followed by 9×10^6 IU days 3-5. On days 6 and 7 no treatment is administered. After 1 week without PROLEUKIN therapy, this 4-week cycle should be repeated.
Maintenance: The same cycle as described above may be given to patients who respond or have disease stabilisation.
If the patient does not tolerate the recommended dosage regimen, the dose should be reduced or the administration interrupted until the toxicity has moderated. It is not known to what extent dose reduction affects the response rate and median survival.

Renal or hepatic impairment
No formal studies have been conducted to evaluate the pharmacokinetics, safety and tolerability of PROLEUKIN in patients with pre-existing renal or hepatic impairment (see section 4.4).

Elderly patients:
No formal clinical studies were conducted to compare the pharmacokinetics, efficacy or safety of PROLEUKIN in geriatric patients to those in younger patients. There were a very small number of patients aged 65 and over in clinical trials of PROLEUKIN. Clinicians should exercise caution in prescribing PROLEUKIN in elderly patients since a decline in renal and hepatic function may occur with increasing age. Hence, elderly patients may be more susceptible to the side effects of PROLEUKIN (see sections 5.1 and 5.2).

Paediatric population:
The safety and efficacy of PROLEUKIN in children and adolescents has not yet been established."

06 THERAPEUTIC NEED

Kidney cancers account for 2 to 3% of cancers in adults.[1] Histologically, 70 to 75% of these are clear-cell tumours. Since the advent of so-called targeted therapies, the median survival time for metastatic renal cell carcinoma is estimated to be 40 months.[2]

The aim when treating advanced stage renal cell carcinoma is to improve overall survival and quality of life.
The treatment algorithm for metastatic renal cell carcinomas is based mainly on the identification of prognostic factors for the disease using the MSKCC classification,[3] which was established in the era of immunotherapy but still remains the reference. It can be used to define three prognostic groups based on clinical and biological criteria: general condition (Karnofsky index), the time between the initial diagnosis and first-line treatment, the LDH and haemoglobin levels and the corrected serum calcium level. According to these criteria, patients are grouped into three categories: good prognosis (0 criterion present), intermediate prognosis (1 or 2 criteria) and poor prognosis (> 3 criteria)
Until 2006, the treatment options essentially consisted of immunotherapy (interleukin-2 and interferon-alpha).

Since the arrival of so-called targeted therapies in 2006, the treatment of metastatic renal cell carcinoma has changed profoundly. The role of immunotherapy represented by two cytokines: aldesleukin (PROLEUKIN) or interferon alfa (ROFERON-A) has become very limited. The first-line treatment is sunitinib (SUTENT) used in approximately 2/3 of patients or the combination bevacizumab (AVASTIN)/interferon alfa (ROFERON-A) in patients with a good or intermediate prognosis and temsirolimus (TORISEL), an mTOR inhibitor, in patients with a poor prognosis.

[1] Rini B, Campbell S, Escudier B. Renal cell carcinoma. Lancet 2009; 373 (9669): 1119-1132.
[2] Thuret R et al. Treatment of metastatic renal cell carcinoma. Progrès en Urologie. 2011; 21: 233-244.
[3] Memorial Sloan-Kettering Cancer Center.

07 CLINICALLY RELEVANT COMPARATORS

07.1 Medicinal products

Another cytokine has Marketing Authorisation for the treatment of advanced renal cell carcinoma: ROFERON-A (interferon alfa-2a). The dosage section of the SPC for ROFERON-A provides for its use in combination, especially with AVASTIN. Indeed, since December 2007, AVASTIN (bevacizumab) in combination with interferon alfa-2a has had Marketing Authorisation as first-line treatment in adult patients with advanced and/or metastatic renal cell carcinoma.

For information, the proprietary medicinal product ROFERON-A is not included on the list of chargeable medicinal products in addition to hospital services.

NAME (INN) *Company*	Same TC* Yes/No	Date of opinion	AB	IAB (Wording)	Reimbursement Yes/No
ROFERON A Interferon alfa-2a Roche	Yes	3/09/2008: inclusion of the AVASTIN (bevacizumab) + interferon combination	Substantial	IV compared to interferon alfa alone, in terms of efficacy	Yes
		18/07/2012 (renewal of inclusion)	Substantial in the targeted indications	Not available	Yes

*therapeutic category

07.2 Other health technologies

Not applicable

◗ Conclusion

ROFERON-A (interferon alfa-2a) is not a clinically relevant comparator because its combination with AVASTIN has a different role in the therapeutic strategy.

08 INTERNATIONAL INFORMATION ON THE MEDICINAL PRODUCT

In the United States, PROLEUKIN has two Marketing Authorisation indications in adults in the treatment of:

- metastatic melanoma,
- metastatic renal cell carcinoma with a different dosing regimen to those validated in France: intravenous bolus route (0.6 x 10^6 IU/kg every 8 hours as an IV bolus for a maximum of 28 doses).

Country	Reimbursement	
	Yes/ No	Scope (indications) and special condition(s)
Europe (Austria, The Netherlands, Belgium, Denmark, Finland, Germany, Greece, Iceland, Italy, Ireland, Luxembourg, Portugal, Spain, The United Kingdom)	Yes	Treatment of metastatic renal cell carcinoma
Canada	Yes	PROLEUKIN (aldesleukin) is indicated for the treatment of adults (≥18 years of age) with metastatic renal cell carcinoma (metastatic RCC). PROLEUKIN is indicated for the treatment of adults (≥18 years of age) with metastatic malignant melanoma (metastatic MM).

09 SUMMARY OF PREVIOUS ASSESSMENT

◗ Re-assessment of the IAB (referral from the Ministry of Health)

Date of opinion (reason for the review)	2 February 2005 (re-assessment of AB)
AB	Cancers are common diseases, usually severe and which are life-threatening. These proprietary medicinal products are intended as curative, palliative or adjuvant therapy Their efficacy is established. These proprietary medicinal products are essential in the treatment of these pathologies. Generally, these proprietary medicinal products are used in poly-chemotherapy regimens or in combination with surgery or radiotherapy. These proprietary medicinal products are first- or second-line medicines, depending on the type of cancer The choice of antineoplastic proprietary medicinal products and their role in the therapeutic strategy is based on the characteristics of the cancer (type, nature, localisation of the tumour, if other organs are affected or not, etc.) and those of the patient (age, general condition, response to treatment, etc.). The adverse effects of anticancer treatment depend on their therapeutic class and are related to their toxicity to normal cells [...]. The actual benefit of these proprietary medicinal products in all indications is substantial.
IAB	Unspecified
Target population	Unspecified

Furthermore, on 26 November 2008, the Transparency Committee issued a favourable opinion on the delisting of medicinal products approved for hospital use (following the invalidation of the Marketing Authorisation on 06/10/2006) for the proprietary medicinal product PROLEUKIN 9 million IU, powder for solution for injection.

10 ANALYSIS OF AVAILABLE DATA

As part of the assessment of PROLEUKIN, the company provided a clinical dossier including four non-comparative studies:
- for the continuous IV route: 2 phase II studies (EC-L2-008 and EC-MP-001)
- for the SC route: two studies (EC-MP-101[4] and NL-MP-100[5]).

It should be emphasised that these studies included patients with a heterogeneous risk profile, especially those with a poor prognosis risk (> 50% had an ECOG score of 1, approximately 50% had metastases in more than two organs and more than two thirds had a delay of less than 24 months between the time diagnosis and the start of treatment. The results are only available in the total study population. Therefore, there is no specific efficacy data in the smaller subgroup of patients validated by the Marketing Authorisation in 1992 (according to the current wording of the indication of the Marketing Authorisation and the clinical recommendations).

For information, the company did not provide the five non-comparative studies presented in the initial Marketing Authorisation dossier for PROLEUKIN from 1988 to the extent that they no longer correspond to:
- the dosage validated by the current Marketing Authorisation: two of the five studies PROLEUKIN administered as an intravenous bolus (historically, interleukin-2 had been evaluated at high-doses as an intravenous bolus);
- the current practice: four studies out of five evaluated the combination of PROLEUKIN with LAK cells (Lymphokine Activated Killer Cells).

Furthermore, an additional literature search of the data provided by the company has identified direct comparison studies between PROLEUKIN and interferon alfa, its clinically relevant comparator. Only one publication[6] that, although not specifically performed in the restricted population validated by the Marketing Authorisation for PROLEUKIN, likely to provide comparative data is presented for information purposes in paragraph 10.1.3.

10.1 Efficacy

10.1.1 Administration by continuous intravenous (IV) infusion

The company presented the results from two phase II non-comparative studies (EC-L2-008 and EC-MP-001) performed with a similar methodology described below.
The primary endpoint was to evaluate the efficacy and safety of aldesleukin administered as a continuous intravenous infusion in patients with metastatic renal cell carcinoma, previously treated or untreated with chemotherapy or immunotherapy

Dosage
Aldesleukin (PROLEUKIN) was administered by continuous IV infusion at a dosage of 18×10^6 IU/m^2/day:
- For the induction therapy:
  - from D1 to D5 in the EC-L2-008 study or from D1 to D6 in the EC-MP-001 study then
  - from D12 to D16 (EC-L2-008 study) or from D8 to D12 (EC-MP-001 study).

  A second induction cycle was administered after 3 weeks.

[4] Tourani JM, Lucas V Mayeur D et al. Subcutaneous recombinant interleukin-2 (rIL-2) in out-patients with metastatic renal cell carcinoma. Ann Oncol 1996; 7: 525-528.
[5] Nieken J, Sleijfer DT, Buter J et al. Outpatient-based subcutaneous interleukin-2 monotherapy in advanced renal cell carcinoma: an update. Cancer Biother Radiopharm 1996; 11(5): 289-295.
[6] Negrier S, Escudier B, Lasset C, Douillard JY, Savary J, Chevreau C, et al. Recombinant human interleukin-2, recombinant human interferon alfa-2a, or both in metastatic renal cell carcinoma. Groupe Français d'Immunothérapie. N Engl J Med 1998; 338: 1272-8.

- For the maintenance treatment: after 3 weeks, from D1 to 6 for a 4-week cycle. This cycle could be repeated for a maximum of four cycles only in the EC-MP-001 study.

Endpoints
- response rate defined according to the WHO criteria,
- overall survival,
- progression-free survival.

Results

◗ EC-L2-008 study

In total, 97 patients with metastatic renal cell carcinoma who had not received prior treatment with chemotherapy or immunotherapy were included between December 1987 and June 1989 in 12 centres and between July 1989 and June 1990 for two centres (84 patients evaluable for efficacy).
At baseline, the average age of patients was 58 years and 64% of patients were men. The patients were in good general condition (ECOG score of 0: 47% and ECOG score of 1: 53%). The average time between initial diagnosis of the primary tumour and the start of treatment with aldesleukin (PROLEUKIN) was 2.1 months and this delay was greater than 24 months for 21%. More than two thirds of patients (76%) underwent a nephrectomy beforehand. The number of metastatic disease sites per patient varied between 1 (22%) to more than 3 sites.

The objective response rate (CR + PR) was 16% with 5% of CR (4 patients). The overall median survival was 270 days. The median progression-free survival was 245 days in the 14 patients with a complete or partial response and in the 22 patients with stable disease.

◗ EC-MP-001 study

Between March 1989 and June 1990, 185 patients with renal cell carcinoma, who either did or did not previously receive chemotherapy or immunotherapy were treated (109 patients evaluable for efficacy).
At baseline, the average age of patients was 56 years and 73% of patients were men. The patients were in good general condition (ECOG score of 0: 38% and ECOG score of 1: 62%). The average time between initial diagnosis of primary tumour and the start of treatment with aldesleukin (PROLEUKIN) was 9.5 months, and this delay was greater than 24 months for 14%. More than two thirds of patients (77%) underwent a nephrectomy beforehand. The number of metastatic disease sites per patient varied between 1 (41%) to more than 3 sites.

The objective response rate (CR + PR) was 14% with 4% of CR (4 patients). The overall median survival was 293 days. The median progression-free survival was 273 days in the 15 patients with a complete or partial response and in the 45 patients with stable disease.

10.1.2 Administration by subcutaneous (SC) injection

The company presented the results from two phase II non-comparative studies (EC-MP-101 et NL-MP-100) performed with a similar methodology. To the extent that these studies were conducted with dosing regimens that cannot be strictly superimposed on the regimen validated by the Marketing Authorisation, they will only be described below for information purposes.

The primary endpoint was to evaluate the efficacy and safety of aldesleukin administered by subcutaneous injection in outpatient care in patients with metastatic renal cell carcinoma, previously treated or untreated with chemotherapy or immunotherapy.

Endpoints

- objective response rate: complete response (CR) defined by the disappearance of all clinical or radiological signs of the tumour for at least 4 weeks; partial response (PR): decrease of 50% or more of the measurable lesions for at least 1 month,
- overall survival,
- progression-free survival.

◗ EC-MP-001 study[4]

Dosing regimen

As an induction therapy, PROLEUKIN was administered subcutaneously at a dosage of 9 x 10^6 IU twice a day for the first 5 days of week 1 and 6. During weeks 2, 3, 4, 7, 8 and 9, a dosage of 9 x 10^6 IU twice a day was administered the first 2 days of the week, followed by a dosage of 9 x 10^6 IU/d the 3 following days.
After a 2 week period without treatment, the patients with no disease progression or unacceptable toxicity would receive a maintenance treatment at the same dosage as that of the first 4 weeks of induction. Patients could receive a maximum of seven cycles, with 2 weeks without injection between each cycle.
This administration regimen is not superimposable to that of the Marketing Authorisation:

- 9 x 10^6 IU twice a day instead of 18 x 10^6 IU once a day
- 9 x10^6 IU twice a day from D3 to D5 during week 6 instead of 9 x 10^6 IU once a day
- inter-treatment interval of 2 weeks instead of one, as validated by the Marketing Authorisation.

Results

Between April 1993 and April 1994, 39 patients with metastatic renal cell carcinoma who had not received prior treatment with chemotherapy or immunotherapy were treated. At baseline, the average age of patients was 58 years and the majority of patients were men (77%). The patients were mostly in good general condition (ECOG score of 0: 57%, ECOG score of 1: 33% and ECOG score of 2: 10%). Less than 10% of patients had no adverse adverse prognostic factors (3/39) and 38% had only one. The average time between initial diagnosis of the primary tumour and the start of treatment with aldesleukin (PROLEUKIN) was longer than one year for 45% of patients. All patients underwent a nephrectomy beforehand. About half of the patients had one metastasis (19/39).

The objective response rate (CR + PR) was 18% (7/39) with 3% of CR (1 patient). Among the 24 of the 39 patients treated who had an objective response or stabilisation of the tumour after induction therapy, 17 patients received the maintenance treatment which was discontinued in 11 patients.
With a median follow-up of 19 months, the percentage of overall survival was 65% at 12 months and 33% at 24 months and the average duration of response was 11 months.

◗ NL-MP-100 study[5]

Dosing regimen

PROLEUKIN was administered subcutaneously at a dosage of 18 x 10^6 IU/d for the first 5 days. The following weeks, PROLEUKIN was administered at a dosage of 9 x 10^6 IU/d for the first 2 days and at a dosage of 18 x 10^6 IU/d the following 3 days. The patients could receive two 6-week treatment cycles or three 4-week cycles.
The first 29 patients included received PROLEUKIN by self-injection the first 5 days of the week for 6 weeks, followed by a 3-week period without injection. For the other patients, the cycles were shortened to 4 weeks of 5 days of treatment, followed by 2 weeks without injection in order to reduce toxicity.
This administration regimen is not superimposable to that of the Marketing Authorisation:

- 6-week cycle for the first 29 patients included instead of 4 weeks
- 9 x 10^6 IU/d on D1 and D2 instead of 18 x 10^6 IU/d
- 18 x 10^6 IU/d on D3 to D5 instead of 9 x 10^6 IU/d
- inter-treatment interval of 2 or 3 weeks instead of one, as validated by the Marketing Authorisation.

Results

Between December 1989 and December 1994, 80 patients with metastatic renal cell carcinoma who had not received prior treatment with chemotherapy or immunotherapy were treated (77 patients evaluable for efficacy).

At baseline, the average age of patients was 58 years and the majority of patients were men (51/80). The patients were mostly in good general condition (ECOG score of 0: 54%, ECOG score of 1: 35% and ECOG score of 2: 11%). The average time between initial diagnosis of the primary tumour and the start of treatment with aldesleukin (PROLEUKIN) was longer than 1 year for 45% of patients. More than two thirds of patients (66%) underwent a nephrectomy beforehand. The majority of patients had one metastasis (60%).

The median follow-up time is not available. The objective response rate (CR + PR) was 12% (9/77) with 4% of CR (3 patients). The overall median survival was 12 months. The median progression-free survival was 4 months.

◗ Other information

In the USA, low-dose PROLEUKIN administration, via the subcutaneous route, is not validated. It is only validated for high-dosage intravenous bolus (since 1992). In fact, the American SPC states that low doses of SC PROLEUKIN are not effective based on the results of the NL-MP-100 study (described above) which corresponds to a post-Marketing Authorisation commitment requested by the FDA in order to obtain clinical information about lower doses of PROLEUKIN. In this non-comparative study carried out in 65 patients with metastatic renal cell carcinoma, the dosing regimen for PROLEUKIN was different from that validated by the Marketing Authorisation in France. PROLEUKIN was administered subcutaneously for 5 days during the first week at a dosage of 18 x 10^6 IU. Then, PROLEUKIN was administered on D1 and D2 at a dosage of 9 x 10^6 IU (instead of 18 x 10^6 IU according to the French SPC) and from D3 to D5 at a dose of 18 x 10^6 IU (instead of 9 x 10^6 IU according to the French SPC) during 3 weeks followed by 1 week without treatment with a maximum of 3 cycles (n=40) or during 5 weeks followed by 3 weeks without treatment with a maximum of 2 cycles (n=25).

The American SPC states that the responses observed with these low doses were considerably weaker and short lasting than those observed with the regimen validated for the intravenous bolus route (0.6 x 10^6 IU/kg every 8 hours as an IV bolus for a maximum of 28 doses).

10.1.3 Other data

Following an additional bibliographic search of the data provided by the company, one publication[7] likely to provide data versus interferon-alfa was identified.

In the publication of Négrier 1998, 425 patients with metastatic renal cell carcinoma were randomised to receive either:

- group 1 (n=138): PROLEUKIN (interleukin-2) as an continuous intravenous injection, at a dosage of 18 x 10^6 IU per m^2 according to the recommended dosage in the Marketing Authorisation with the exception of a 3-week interval without treatment for the maintenance cycles instead of 4 weeks according to the Marketing Authorisation.
- group 2 (n=147): ROFERON-A (interferon alfa-2a) administered via the subcutaneous route at a dosage of 18 x 10^6 IU per day 3 times per week for 10 weeks (induction therapy) followed by 13 additional weeks (maintenance treatment)
- group 3 (n=140): PROLEUKIN + ROFERON-A. As this combination has not been validated by the Marketing Authorisation, it will not be described.

In the event of progression, a crossover was authorised for groups 1 and 2.

The primary efficacy endpoint was the objective response rate.

[7] Negrier S, Escudier B, Lasset C, Douillard JY, Savary J, Chevreau C, et al. Recombinant human interleukin-2, recombinant human interferon alfa-2a, or both in metastatic renal cell carcinoma. Groupe Français d'Immunothérapie. N Engl J Med 1998; 338: 1272-8.

At baseline, between March 1992 and July 1995, 72% of patients from the PROLEUKIN group and 77% from the ROFERON-A group had an ECOG score of 0; 22% of patients from the PROLEUKIN group and 28% from the ROFERON-A group had one metastatic site. More than 90% of patients underwent a nephrectomy beforehand.

At week 10, the objective response rate was 6.5% (9/138) in the PROLEUKIN group with two complete responses and 7.5% (11/147) in the ROFERON-A group without complete response.
At week 25, after administration of the maintenance treatment in 29 patients from the PROLEUKIN group and in 59 patients from the ROFERON-A group, the response rate was 2.9% (4/138) in the PROLEUKIN group with a complete response and 6.1% (9/147) in the ROFERON-A group with two complete responses.
With a median follow-up of 39 weeks, the progression-free survival rate was 15% in the PROLEUKIN group and 12% in the ROFERON-A group. Overall survival did not differ between the groups (in particular, 12 months in the PROLEUKIN group and 13 months in the ROFERON-A group).
Adverse events were more common in patients treated with PROLEUKIN than in patients from the ROFERON-A group. The grade 3 or 4 events most frequently observed were hypotension (94/138) and fever (59/138) in the PROLEUKIN group and deterioration of the general condition (23/147) in the ROFERON-A group.

In the absence of any clarification about the primary endpoint and the methodology of the study in this publication and knowing that we do not have the study report, no formal conclusions can be drawn.

10.2 Safety/Adverse effects

10.2.1 Data from studies

◗ Administration by continuous intravenous infusion

Treatment discontinuations due to adverse events affected 9% of the patients (8/92) in the EC-L2-008 study and 17% (23/133) in the EC-MP-001 study.
The most common adverse events in the EC-L2-008 and EC-MP-001 study, respectively, were:
- hypotension (93%; 54%), grade 4 in 10 patients (11%; 5%)
- fever (91%; 94%)
- anaemia (85%; 72%)
- increase in blood creatinine levels (82%; 55%)
- increase in alkaline phosphatase levels (74%; 50%)
- nausea and vomiting (71%; 51%).

In the EC-L2-008 study, 10 out of 92 patients died during the month following the last dose of PROLEUKIN:
- 6 from a cause related to the pathology,
- 2 from catheter-related septicaemia,
- in two patients, the relationship between PROLEUKIN and death could not be ruled out (increased creatinine levels and death from multiple organ failure associated with seizures; onset of confusion and fluid retention, and death within the context of renal impairment).

In the EC-MP-001 study, among the 14 patients who died in the month following the last dose of PROLEUKIN, 4 were potentially related to PROLEUKIN (grade 4 hypotension with impaired consciousness; grade 4 pulmonary oedema; hypercalcaemia; secondary massive pulmonary embolism).

◗ Administration by subcutaneous (SC) injection

The most common adverse events were:
- local reaction at the injection site: moderate erythema and local infiltration (100%) in the NL-MP-100 study (n=80), painful swelling (64%) in the EC-MP-101 study (n=39)
- fever (100% in the two studies),

- nausea and vomiting (84%; 54%),
- diarrhoea (43% in the NL-MP-100 study),
- anorexia (87%), asthenia (82%), skin toxicity (33%) in the EC-MP-101 study.

In the NL-MP-100 study, treatment discontinuations affected 3 of the 80 patients (myocardial infarction followed by death; appearance of new signs of paralysis in a patient with a spinal cord compression of metastatic origin; renal impairment).

In the EC-MP-101 study, 5 of the 39 patients did not continue the study and during induction therapy, the dose of PROLEUKIN was decreased or treatment was discontinued due to toxicity in 7 of the 39 patients included: neuropsychiatric manifestations (3 patients), stroke (1), septicaemia (1), joint pain (1), asthenia and major anorexia (1).
These adverse events were most often grade 1 or 2. A grade 4 fever occurred in two patients.

10.2.2 SPC data

The frequency and severity of adverse reactions to PROLEUKIN are dependent on route of administration, dose and dosing regimen.
Most adverse events could disappear 1 to 2 days after discontinuation of treatment. The rate of treatment-related deaths in the 255 metastatic renal cell carcinoma patients who received high-dose PROLEUKIN monotherapy as an IV bolus (dosage not validated in France) was 4% (11/255). In patients on subcutaneous treatment, less than 1% died due to adverse reactions.

The adverse reactions very commonly reported (≥ 1/10), in clinical studies and post-marketing, were:

- anaemia, thrombocytopaenia
- hypothyroidism
- anorexia
- anxiety, confusion, depression, insomnia
- vertigo, headache, paraesthesia, drowsiness
- tachycardia, arrhythmia, thoracic pain
- hypotension
- dyspnoea, cough
- nausea with or without vomiting; diarrhoea; stomatitis
- erythema, rash, exfoliative dermatitis, pruritus, sweating
- renal impairment
- reactions at the injection site, pain at the injection site, inflammation at the injection site, with lower frequency when administered by continuous intravenous infusion.
- fever with or without chills, malaise, asthenia and fatigue, pain, oedema, weight gain or loss.

Among the particular adverse events:
<u>Capillary leak syndrome</u>
Capillary leak syndrome (CLS) has been reported after administration of PROLEUKIN; it is characterised by a loss of vascular tone and extravasation of plasma proteins and fluid into the extravascular space. This capillary leak syndrome causes hypotension, tachycardia and hypoperfusion of organs. A severe case of CLS leading to death has been reported.
Cardiac arrhythmias (supraventricular and ventricular), angina pectoris, myocardial infarction, respiratory insufficiency requiring intubation, gastrointestinal bleeding, mesenteric infarction, renal insufficiency, oedema and mental status changes may be associated with capillary leak syndrome (see section 4.4). The frequency and severity of capillary leak syndrome are lower with subcutaneous administration than with continuous intravenous infusion.

<u>Bacterial infections</u>

Bacterial infection or exacerbation of bacterial infections, including septicaemia, bacterial endocarditis, septic thrombophlebitis, peritonitis, pneumonia, and local infection in the catheter have been reported primarily after intravenous administration (see section 4.4).

Severe eosinophilia
During treatment, most patients experience lymphocytopaenia and eosinophilia with a rebound lymphocytosis within 24 to 48 hours following treatment. Severe manifestations of eosinophilia have been reported, involving eosinophilic infiltration of cardiac and pulmonary tissues.

Cerebral vasculitis
Cerebral vasculitis, isolated or in combination with other manifestations, as well as cutaneous and leukocytoclastic hypersensitivity vasculitis have been reported. Some of these cases are responsive to corticosteroids.

10.3 Usage/prescription data

Given the small number of sales, the conditions of use of PROLEUKIN cannot be documented from prescription panels.
For information purposes, annual GERS [Group for the production and implantation of statistics] hospital sales data (in CUD), from 2006 to 2013, are presented in the following table:

Table: GERS sales data, in number of boxes

Wording	2006	2007	2008	2009	2010	2011	2012	2013
PROLEUKIN 18 M IU FL INJ *(IV route)*	1095	3542	2057	1267	959	1185	1422	2421
PROLEUKIN 18 M IU FL INF *(SC route)*	173	499	387	487	410	316	169	216
TOTAL	1268	4041	2444	1754	1369	1501	1591	2637

As a reminder, the dosing regimen recommended by the Marketing Authorisation for the continuous IV route includes two induction cycles (corresponding to 20 administrations of 18 x 10^6 IU per m^2) and up to four maintenance cycles (20 administrations of 18 x 10^6 IU per m^2) in the event of response or disease stabilisation. Taking 1.73 m^2 as the average body surface area, the 40 administrations of 18 x 10^6 IU per m^2 would require approximately 68 vials per patient, without dose adjustment and considering that there is no loss during reconstitution and dilution.[8] Thus, the 2421 vials sold in 2013 correspond roughly to the treatment of 36 patients.

[8] The SPC indicates a shelf-life of 24 hours after reconstitution and that the diluted solution should be used within 48 hours after reconstitution, including the infusion period.

10.4 Summary & discussion

The available data that can be used to establish the efficacy and safety of PROLEUKIN in metastatic renal cell carcinoma are limited and provide a law level of evidence.
In four phase II non-comparative studies carried out in a larger population than the one currently validated by the Marketing Authorisation, the objective response rate for PROLEUKIN, via the continuous intravenous or subcutaneous route, was low (of the order of 15% with less than 5% of complete response). The median overall survival was 9 months in studies performed with continuous intravenous PROLEUKIN.
The amount of effect of PROLEUKIN in the population that is smaller than the one of the Marketing Authorisation, which in particular excludes patients with three factors combined with decreased response rates and median survival (ECOG ≥ 1, more than one organ with metastatic disease sites, period of < 24 months between initial diagnosis of the primary tumour and the date the patient is assessed for PROLEUKIN treatment), is difficult to assess to the extent that the results are only available in the total population of the studies.
These studies were conducted in the 1990s, before the arrival of the so-called targeted therapies that are currently the first-line treatment of metastatic renal cell carcinoma. Thus, no efficacy and safety data for second-line PROLEUKIN are available in patients treated with the currently recommended first-line standard.

The frequency and severity of adverse reactions to PROLEUKIN are dependent on route of administration, dose and dosing regimen. The most frequently reported adverse events were hypotension, fever and anaemia for the intravenous route and local reactions at the injection site, fever, nausea and vomiting for the subcutaneous route. The primary particular adverse events were onset or exacerbation of bacterial infections (including septicaemia, bacterial endocarditis) and capillary leak syndrome, characterised by a loss of vascular tone, extravasation of plasma proteins and fluid in the extravascular space and causing hypotension, tachycardia and hypoperfusion of organs.

Quality of life data are not available.

10.5 Planned studies

No ongoing or future study has been cited by the company.

11 THERAPEUTIC USE

In patients with a good or intermediate prognosis, the first-line treatments are: sunitinib (SUTENT) used in approximately 2/3 of patients or the combination bevacizumab (AVASTIN)/interferon alfa (ROFERON-A).
Pazopanib (VOTRIENT) also has Marketing Authorisation (June 2010) in advanced renal cell carcinoma in VOTRIENT 1st-line and represents a first-line treatment of advanced stage renal cell carcinoma. However, the Transparency Committee estimated that its IAB was low in this indication given the level of proven efficacy (opinion of 26/06/2013).

In patients with a poor prognosis, the recommended treatment is temsirolimus (TORISEL), an mTOR inhibitor.

According to the French[9] and European recommendations,[10,11] cytokines (including high-dose interleukin-2, not validated in France) remain a first-line treatment option in the management of

[9] Patard J-J, Baumert H, Bensalah K, et al. Recommandations en onco-urologie 2013 du CCAFU : Cancer du rein. Prog Urol 2013; (suppl. 2): S177-S204.
[10] Escudier B, Eisen T, Porta et al. Renal cell carcinoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2012; 23 (suppl. 7): 65-71.

clear-cell metastatic renal cell carcinoma. The American recommendations NCCN 2014 are not taken into account to the extent that they only cite the high-dose administration schedule with PROLEUKIN via an IV bolus which is not validated in France. The available recommendations[9,10] cite cytokines without distinguishing or favouring one over the other.

Since the arrival of so-called targeted therapies, the role of PROLEUKIN has been marginalised in the therapeutic strategy; it is limited to a selected subset of patients with a good prognosis as defined by the French immunotherapy group: patients in good general health (Karnofsky index > 80%) and with a single metastatic site (usually pulmonary),[12,13] in first-line treatment.

12 TRANSPARENCY COMMITTEE CONCLUSIONS

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

12.1 Actual benefit

- Metastatic renal cell carcinoma is a serious and life-threatening disease.
- These medicinal products are intended as specific curative cancer therapy.
- The efficacy/adverse effects ratio is regarded as low.
  - Public health benefit:

    In France, the public health burden of renal cell carcinoma can be regarded as moderate (approximately 11,500 new cases in 2012). In terms of mortality, it accounts for about 2.5% of all deaths from cancer. That concerning the subpopulation of patients with metastatic renal cell carcinoma who are likely to benefit from first-line treatment with PROLEUKIN can only be small.

    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).

    Given the low response rates obtained in non-comparative studies conducted in a heterogeneous group of patients and the safety profile, the impact of PROLEUKIN in terms of morbidity and mortality can only be small at best. No data can be used to assess the impact of this proprietary medicinal product in terms of quality of life.

    The transferability of the results, from old and non-comparative studies, to clinical practice is not ensured given the development of the therapeutic strategy and limited role of cytokines.

    No impact on the organisation of care is expected.

    The proprietary medicinal product PROLEUKIN is therefore unlikely to meet any identified public health need.

    Consequently, this proprietary medicinal product cannot have an impact on public health.

- This is a first-line treatment option, for a limited subgroup of selected patients with good prognosis.
- There is no treatment alternative in this situation.

Taking account of these points, the Committee considers that the actual benefit of PROLEUKIN is low in the Marketing Authorisation indication.

12.2 Improvement in actual benefit (IAB)

[11] Ljungberg B, Bensalah K, Bex A, et al. Guidelines on renal cell carcinoma. European Association of Urology 2014 http://www.uroweb.org/gls/pdf/10%20Renal%20Cell%20Carcinoma_LR.pdf.

[12] Negrier S, Escudier B, Lasset C, Douillard JY, Savary J, Chevreau C, et al. Recombinant human interleukin-2, recombinant human interferon alfa-2a, or both in metastatic renal cell carcinoma. Groupe Français d'Immunothérapie. N Engl J Med 1998; 338: 1272-8.

[13] Méjean A.Lebret T. Prise en charge du cancer renal métastatique Progrès en urologie 2008, 298-308.

In view of:
- The limited available data (old, uncontrolled studies)
- the absence of specific data in the current Marketing Authorisation population and for the validated dosages,

but considering that PROLEUKIN may have a (marginal) role in the therapeutic strategy,
the Committee considers that these proprietary medicinal products do not provide any improvement in actual benefit (level V, non-existent) in the current management of patients with metastatic renal cell carcinoma.

12.3 Target population

The target population of PROLEUKIN (aldesleukin) is represented by the selected patients with metastatic renal cell carcinoma, with a good prognosis and in the first-line of treatment. This target population is difficult to quantify in the indication of the Marketing Authorisation and in view of its limited role in the therapeutic strategy.

However, it can be approximated from the following data:
- for 2012, a projection by the InVS [French National Health Monitoring Institute] estimates that in France there were 11,573 new cases of renal cell carcinoma,
- clear-cell renal cell carcinoma accounts for 70% to 85% of renal cancers,[14] i.e. between 7764 and 9428 patients.
- epidemiological data to accurately estimate the proportion of patients with metastatic renal cell cancer are not available. A range of 30 to 50% will be used for the calculation.[15] Therefore, the number of first-line patients at the metastatic stage is between 2330 and 4714 first-line patients per year.
- we do not have any exact data on the proportion of patients who received 1st-line treatment with cytokine.

  It should be noted that in the calculation of the target population for INLYTA as second-line treatment after failure of cytokine, the Transparency Committee considered that due to the marginalised use of cytokines in first-line treatment, the population of patients with failure to this line and who received treatment with INLYTA could not be quantified.

  However, the proportion of patients eligible for a first-line cytokine can be approximated from the results of a market study cited in the Transparency Committee's opinion relative to INLYTA dated 9 January 2013 (see description in annex) which states that only 0.3% of patients were treated with drugs other than SUTENT, TORISEL, VOTRIENT, AVASTIN ± IFN, NEXAVAR and AFINITOR. By rounding this proportion to 1%, approximately between 23 and 47 patients could be eligible for a cytokine.

  Furthermore, these data are consistent with older data from a market survey (performed at the end of 2008 start of 2009 for NOVARTIS) cited in the Transparency Committee's opinion relative to AFINITOR dated 13 January 2010, which showed in particular that 2.6% of patients under treatment received an interleukin (see description in Annex 2), within a context where the therapeutic strategy has changed since the arrival of tyrosine kinase inhibitors in 2007 for the first-line treatment.

The total estimated target population for PROLEUKIN is less than 50 patients per year.

13 TRANSPARENCY COMMITTEE RECOMMENDATIONS

The Committee recommends continued inclusion on the list of medicines approved for hospital use in the indication and at the dosage in the Marketing Authorisation.

[14] Escudier, T. Eisen, C. Porta J. J. Patard, Renal cell carcinoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Annals of Oncology 23 (Supplement 7): 65-71, 2012.
[15] Méjean A et Lebret T. Prise en charge du cancer rénal métastatique. Prog Urol 2008; (suppl. 7): S298-S308.

APPENDIX 1[16]

Survey carried out between 5 January 2012 and 30 March 2012 in five countries (Germany, UK, France, Spain and Italy) among 589 doctors, including 116 French doctors (87% oncologists and 13% urologists). These practitioners worked at a university hospital (31%), a university/general hospital (31%), a private institution (19%) or a cancer centre (18%).
Each practitioner had to supply the data for the last three patients treated with chemotherapy or targeted therapy (whatever the line of treatment) and the data for two patients who received second- or third-line treatment.

Overall, the results of this survey are taken from the retrospective analysis of the data for 2397 patients (468 of them in France) with metastatic renal cell carcinoma who were undergoing treatment (irrespective of the line) and for 1096 patients (214 of them in France) receiving second-line treatment during the survey.

The patients' mean age was 63.7 years (64.1 years in France). Patients were in good general condition (ECOG 0) in 32% of cases (24% in France) and had an ECOG 1 in 53% of cases (57% in France). Patients had a favourable prognosis in 34% of cases and an intermediate prognosis in 44% of cases (33% and 41% in France). The proportion of patients who had undergone nephrectomy is not available.

Of the 2397 patients included retrospectively, 1807 were on first-line treatment (352 of them in France) and 69% were being treated with sunitinib (71% in France).
The other medicinal products received in the first-line were:
- TORISEL: 12% (19% in France)
- VOTRIENT: 7% (0% in France)
- AVASTIN ± IFN: 6% (5% in France)
- NEXAVAR: 5% (4% in France)
- AFINITOR: 1% (0.3% in France)
- other products: 0.3% (0% in France)

APPENDIX 2

Survey conducted between 24 November 2008 and 7 January 2009 in France with 70 physicians (84.3% of oncologists). These practitioners worked at a university hospital (29%), a university/general hospital (27%), a private institution (29%) or a cancer centre (16%).
Each physician had to include a maximum of 12 patients under treatment, i.e. currently receiving chemotherapy/immunotherapy and/or targeted therapy, for currently locally advanced/metastatic renal cell carcinoma.

In total, the results of this prospective survey are from the weighted analysis of data from 529 patients with locally advanced or metastatic clear-cell renal cell carcinoma among which 340 were undergoing first-line treatment (64% of which 14 patients treated in a clinical study) and 123 were undergoing second-line treatment (23%).

The mean age of the patients was 64.2 years. Three-quarters of patients were in good general condition (ECOG 0) in 26% of cases and had an ECOG 1 in 48% of cases. More than half of the patients (57%) were diagnosed at the metastatic stage (stage IV). Patients had a favourable prognosis in 30% of cases and an intermediate prognosis in 44% of cases.

Among the 529 patients, 340 were undergoing first-line treatment and 62.2% were treated with sunitinib.
The other medicinal products being administered in the first-line during the survey were (total 1st-line = ongoing or completed 1st-line):

[16] Transparency Committee opinion of 09 January 2013 on INLYTA.

- TORISEL: 19.2% (12.5%)
- AVASTIN: 12.5% (11.1%)
- Interferon: 9.3% (15.7%)
- NEXAVAR: 7.2% (6.9%)
- Interleukins: 2.6% (6.7%)
- clinical study: 0.5% (0.3%)