HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

Opinion
28 May 2014

LONQUEX 6 mg, solution for injection - syringe (glass) 0.6 ml

B/1 pre-filled syringe with security device (CIP: 34009 275 889 9 0)

Applicant: TEVA SANTE

INN	lipegfilgrastim
ATC code (2012)	L03AA14 (colony stimulating factors)
Reason for the 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	**"Reduction in the duration of neutropenia and the incidence of febrile neutropenia in adult patients treated with cytotoxic chemotherapy for malignancy (with the exception of chronic myeloid leukaemia and myelodysplastic syndromes).»**

Actual Benefit	**The actual benefit of LONQUEX is insufficient.**
Therapeutic use	**This proprietary medicinal product has no role in the therapeutic strategy.**
Recommendations	**The Committee does not recommend inclusion on the list of medicines refundable by National Health Insurance or on the list of medicines approved for hospital use in the indication "Reduction in the duration of neutropenia and the incidence of febrile neutropenia in adult patients treated with cytotoxic chemotherapy for malignancy (with the exception of chronic myeloid leukaemia and myelodysplastic syndromes)" and at the dosages in the Marketing Authorisation.**

01 ADMINISTRATIVE AND REGULATORY INFORMATION

Marketing Authorisation (centralised procedure)	25/07/2013 (centralised procedure) The holder of the marketing authorisation will take the following steps, according to the schedule below: Post-marketing safety study to provide an additional evaluation of the risks of disease progression and mortality associated with LONQUEX in patients with a malignancy treated with cytotoxic chemotherapy. The risks must be determined relative to an established comparator and to a placebo and disease progression must be evaluated objectively. A clinical model with adequate sensitivity must be selected to assess the above risks. Submission of final study report: 30/06/2017
Prescribing and dispensing conditions/special status	List I Medicine for initial three month hospital prescription. Initial prescription restricted to specialists in oncology or haematology. Medicinal product requiring special monitoring during treatment.

ATC Classification	2012	
	L	Antineoplastic and immunomodulating agents
	L03	Immunostimulants
	L03A	Immunostimulants
	L03AA	Colony stimulating factors
	L03AA14	lipegfilgrastim

02 BACKGROUND

Review of the application for inclusion of the proprietary medicinal product LONQUEX 6 mg, solution for injection – 0.6 ml (glass) syringe, on the list of medicines refundable by National Health Insurance and on the list of medicines approved for hospital use, at the initiative of the company.

Lipegfilgrastim, the active ingredient of LONQUEX, is a new long-acting granulocyte colony stimulating factor (G-CSF) to prevent and reduce the duration of neutropenia induced by cytotoxic chemotherapy.

03 THERAPEUTIC INDICATIONS

"Reduction in the duration of neutropenia and the incidence of febrile neutropenia in adult patients treated with cytotoxic chemotherapy for malignancy (with the exception of chronic myeloid leukaemia and myelodysplastic syndromes)"

04 DOSAGE

"Posology
One 6 mg dose of lipegfilgrastim (a single pre-filled syringe of LONQUEX) is recommended for each chemotherapy cycle, given approximately 24 hours after cytotoxic chemotherapy.

Special populations
Elderly patients
No adjustment of the dose is necessary for elderly patients.

Patients with renal and/or hepatic impairment
Due to the neutrophil-mediated clearance mechanism, the pharmacokinetics of lipegfilgrastim is not expected to be affected by renal or hepatic impairment.
No recommendation on a posology can be made.

Paediatric population
The safety and efficacy of LONQUEX in children and adolescents aged up to 17 years have not yet been established. No data are available.

Method of administration
The solution is injected subcutaneously (SC). The injections should be given into the abdomen, upper arm or thigh.
The first injection of LONQUEX should be performed under direct medical supervision. "

05 THERAPEUTIC NEED

Cytotoxic chemotherapy entails a substantial risk of haematopoietic system toxicity and can induce severe and prolonged neutropenia. This chemotherapy-induced neutropenia causes infectious complications requiring hospitalisation of the patient and may be life-threatening.[1]
To review, neutropenia is defined as an absolute neutrophil count (ANC) below 1.5 x 10^9/l; febrile neutropenia is defined as an ANC below 0.5 x 10^9/l with fever (axillary body temperature above 38.5°C for at least an hour) or clinical signs of sepsis.[2]

This neutropenia is one of the major toxicities of cancer chemotherapy. It is the main cause of dose reduction or extension of the period between chemotherapy cycles, which compromises their efficacy.

The availability of the first granulocyte colony stimulating factor, filgrastim (NEUPOGEN, marketing authorisation granted in 1991), represented a major breakthrough in reducing the duration and intensity of chemotherapy-induced neutropenia.
The availability of a new granulocyte colony stimulating factor, lenograstim (GRANOCYTE, marketing authorisation granted in 1993) and more recently filgrastim biosimilars (NIVESTIM, RATIOGRASTIM, TEVAGRASTIM, ZARZIO) has enabled alternative therapies to be introduced.
The pegylated formulation of filgrastim (NEULASTA, marketing authorisation granted in 2002) improved the ease of use of filgrastim and patient quality of life by extending its half-life: a single injection per chemotherapy cycle instead of a daily injection.

[1] LONQUEX: EPAR (European public assessment report). 2013
[2] Aapro MS et al. 2010 update of EORTC guidelines for the use of granulocyte-colony stimulating factor to reduce the incidence of chemotherapy-induced febrile neutropenia in adult patients with lymphomas and solid tumours. Eur J Cancer 2011; 47: 8-32

The use of granulocyte colony stimulating factors (G-CSF) in oncology is recommended by the American Society of Clinical Oncology Practice (ASCO[3]), the European Society for Medical Oncology (ESMO[4]) and the European Organisation for Research and Treatment of Cancer (EORTC[2]) (Figure 1) in patients subjected to a protocol with a risk of febrile neutropenia greater than 20% or even 10% in some patients for whom the individual risk factors justify it (in particular, above age 65, advanced stage of the disease, one or more prior episodes of febrile neutropenia, no antibiotic or G-CSF therapy, impaired nutritional status, cytopenia related to invasive spinal tumour, extensive prior treatment(s), including wide area irradiation or combination chemotherapy).

[3] Smith Thomas J. and al. 2006 Update of Recommendations for the Use of White Blood Cell Growth Factors: An Evidence-Based Clinical Practice Guideline. ASCO 2006; 24, number 19

[4] Crawford J et al. Hematopoietic growth factors: ESMO Clinical Practice Guidelines for the applications. Ann Oncol 2010; 21(supplement 5): v248-v251

06 CLINICALLY RELEVANT COMPARATORS

INN (proprietary medicinal product)	Company	Indication	AB (date of last opinion)	IAB (Wording)	Reimbursement
Same therapeutic category: granulocyte colony stimulating factors					
pegfilgrastim (NEULASTA)	AMGEN	Reduction in the duration of neutropenia and the incidence of febrile neutropenia in patients treated with cytotoxic chemotherapy for malignancy (with the exception of chronic myeloid leukaemia and myelodysplastic syndromes)	Substantial 03/09/2008	IAB I: NEULASTA® shares with NEUPOGEN® (filgrastim) a level I IAB for reduction in the duration of neutropenia and the incidence of febrile neutropenia in patients treated with cytotoxic chemotherapy for malignancy (with the exception of chronic myeloid leukaemia and myelodysplastic syndromes). Although no benefit in terms of efficacy or safety was noticed, the Committee emphasises the substantial benefit in terms of ease of use and quality of life with this pegylated form of filgrastim: a single injection per chemotherapy cycle instead of daily administration (11 on average) so there is less need for a personal nurse and no need for repeated blood counts.	Yes

INN (proprietary medicinal product)	Company	Indication	AB (date of last opinion)	IAB (Wording)	Reimbursement
Same therapeutic category: granulocyte colony stimulating factors					
filgrastim (NEUPOGEN)	AMGEN	Reduction in the duration of neutropenia and the incidence of febrile neutropenia in patients treated with cytotoxic chemotherapy for malignancy (with the exception of chronic myeloid leukaemia and myelodysplastic syndromes) and reduction in the duration of neutropenia in patients undergoing myeloablative therapy followed by bone marrow transplantation and having an increased risk of prolonged severe neutropenia. The safety and efficacy are similar in adults and children receiving cytotoxic chemotherapy. Long-term administration of NEUPOGEN® in patients, children or adults, with severe congenital, cyclical or idiopathic neutropenia with a neutrophil count <0.5 x 10^9/l and a history of severe or recurrent infections, in order to increase the neutrophil count and reduce the incidence and duration of infectious episodes.	Substantial 14/09/2011	IAB I: The administration of NEUPOGEN® in patients with cancer or chronic severe neutropenia (congenital, cyclic or idiopathic) was a major therapeutic advance in the early 1990s. Currently, G-CSF growth factors, including NEUPOGEN® still play a major role in the various indications and play the same role in the therapeutic strategy.	Yes
		Mobilisation of peripheral blood progenitor cells in the bloodstream.	Substantial	IAB III: In the indication "mobilisation of PBPCs in normal donors prior to allogeneic PBPC transplantation" NEUPOGEN® provides a moderate improvement in actual benefit (level III) in the therapeutic strategy.	Yes
		Persistent neutropenia (ANC less than or equal to 1 x 10^9/l) in patients with advanced HIV infection, in order to reduce the risk of bacterial infections when other options to manage neutropenia are inappropriate.	Substantial	IAB III: In the indication "treatment of persistent neutropenia in patients with advanced HIV infection" NEUPOGEN® provides a moderate improvement in actual benefit (level III) in the therapeutic strategy.	Yes
filgrastim (NIVESTIM) (biosimilar)	HOSPIRA FRANCE	Same indications as NEUPOGEN®	Substantial for all indications 16/02/2011	IAB V: NIVESTIM®, as a biosimilar, does not provide any improvement in actual benefit (IAB V) relative to NEUPOGEN®	Yes
filgrastim (RATIOGRASTIM) (biosimilar)	TEVA SANTE	Same indications as NEUPOGEN®	Substantial for all indications. 10/12/2008	IAB V: RATIOGRASTIM® 30 MIU and 48 MIU do not provide any improvement in actual benefit (IAB V) relative to NEUPOGEN® 30 MIU and 48 MIU.	Yes

INN (proprietary medicinal product)	Company	Indication	AB (date of last opinion)	IAB (Wording)	Reimbursement
Same therapeutic category: granulocyte colony stimulating factors					
filgrastim (TEVAGRASTIM) (biosimilar)	TEVA SANTE	Same indications as NEUPOGEN®	Substantial for all indications 04/03/2009	IAB V: TEVAGRASTIM® 30 MIU and 48 MIU do not provide any improvement in actual benefit (IAB V) relative to NEUPOGEN® 30 MIU and 48 MIU.	Yes
filgrastim (ZARZIO®) (biosimilar)	SANDOZ	Same indications as NEUPOGEN®	Substantial for all indications 24/06/2009	IAB V: ZARZIO® 30 MIU and 48 MIU do not provide any improvement in actual benefit (IAB V) relative to NEUPOGEN® 30 MIU and 48 MIU.	Yes
Lenograstim (GRANOCYTE®)	CHUGAI	The reduction of the duration of severe neutropenia and its associated complications in patients undergoing established chemotherapy associated with a significant incidence of febrile neutropenia.	Substantial 04/11/2009	IAB I: The administration of G-CSF growth factors, including GRANOCYTE® to cancer patients was a major therapeutic advance in the early 1990s. Currently, G-CSF growth factors, including GRANOCYTE®, still play a major role in the treatment of chemotherapy-induced neutropenia, and play the same role in the therapeutic strategy.	
		Reduction of the duration of neutropenia in patients (with non-myeloid malignancy) undergoing myeloablative therapy followed by bone marrow transplantation and having increased risk of prolonged severe neutropenia.	Substantial	IAB I: For the two other indications concerned: "Mobilisation of PBPCs in patients prior to allogeneic PBPC transplantation" and "reduction of the duration of neutropenia in patients undergoing myeloablative therapy followed by bone marrow transplantation and having increased risk of prolonged severe neutropenia", the Committee considers that both growth factors, including GRANOCYTE® still have an important role and play the same role in the therapeutic strategy.	Yes

INN (proprietary medicinal product)	Company	Indication	AB (date of last opinion)	IAB (Wording)	Reimbursement
Same therapeutic category: granulocyte colony stimulating factors					
		Mobilisation of peripheral blood progenitor cells.	Substantial	IAB III In the indication of mobilisation of PBPCs in normal donors prior to allogeneic PBPC transplantation, GRANOCYTE® provides the same improvement in actual benefit of IAB III as NEUPOGEN®. IAB I: For the two other indications concerned: "Mobilisation of PBPCs in patients prior to allogeneic PBPC transplantation" and "reduction of the duration of neutropenia in patients undergoing myeloablative therapy followed by bone marrow transplantation and having increased risk of prolonged severe neutropenia", the Committee considers that both growth factors, including GRANOCYTE® still have an important role and play the same role in the therapeutic strategy.	Yes

Conclusion

The most relevant comparator is NEULASTA, which is the only long-acting granulocyte colony stimulating factor available and consequently strictly comparable to LONQUEX. The other G-CSFs presented above are short-acting granulocyte colony stimulating factors that can be administered SC or IV and are intended for additional indications to those of LONQUEX.

07 INTERNATIONAL INFORMATION ON THE MEDICINAL PRODUCT

Country	REIMBURSEMENT	
	YES/NO If not, why not	Population(s) That of the Marketing Authorisation or restricted
Germany	YES (100%)	MA indication
United Kingdom	YES (100%)	MA indication
Spain	YES (100%)	MA indication
Italy	YES (100%)	MA indication
Belgium	YES (100%)	Predefined list of tumours (see INAMI site)
Austria	YES (100%)	MA indication
Netherlands	YES (100%)	MA indication
Croatia	YES (100%)	MA indication
Denmark	YES (100%)	MA indication
Finland	YES (100%)	MA indication
Hungary	YES (100%)	Secondary prophylaxis
Ireland	YES (100%)	MA indication
Latvia	YES (100%)	MA indication
Luxembourg	YES (100%)	MA indication
Poland	YES (100%)	MA indication
Sweden	YES (100%)	MA indication
Slovenia	YES (100%)	MA indication
Czech Republic	YES (100%)	MA indication
Greece	YES (100%)	MA indication
Other European countries	Under assessment	

08 ANALYSIS OF AVAILABLE DATA

The evaluation of the efficacy of lipegfilgrastim (LONQUEX) mainly relies on a non-inferiority study versus pegfilgrastim (NEULASTA) in terms of the duration of severe neutropenia (DSN) in chemotherapy cycle 1, conducted in patients with breast cancer of stage[5] II at high risk, stage III or stage IV (study XM22-03).

08.1 Efficacy

8.1.1 Study description

Table 1: Study description

	Study XM22-03
Principal study objective	To demonstrate the non-inferiority of lipegfilgrastim relative to pegfilgrastim in terms of the duration of severe neutropenia in patients with breast cancer undergoing the first cycle of myeloablative chemotherapy.
Method	Double-blind, randomised, pegfilgrastim-controlled phase III study.
Study population	Patients with breast cancer of stage II at high risk, stage III or stage IV (classification according to the *American Joint Committee on Cancer – AJCC*)5
Inclusion criteria	- Men or women ≥ 18 years old. - Breast cancer of stage II at high risk, stage III or stage IV (classification according to the *American Joint Committee on Cancer – AJCC*).5 - Chemotherapy planned for 4 cycles with docetaxel/doxorubicin. - Chemotherapy-naive patients. - ECOG functional index[6] ≤ 2. - Absolute neutrophil count (ANC) ≥ 1.5 x 10^9/l and platelet count ≥ 100 x 10^9/l. - Normal heart, liver and kidney function.
Non-inclusion criteria	- Participation in a clinical trial within 30 days prior to randomisation. - Prior exposure to filgrastim, pegfilgrastim or lenograstim or other G-CSF in clinical development within 6 months prior to randomisation. - Known hypersensitivity to docetaxel or doxorubicin, filgrastim, pegfilgrastim or lenograstim. - Grade 2 or higher neuropathy. - Systemic antibiotic treatment within 72 hours prior to chemotherapy. - Lithium treatment. - Chronic oral corticosteroid treatment. - Tumour radiotherapy or surgery within 4 weeks prior to randomisation.

[5] Breast cancer staging - American Joint Committee on Cancer. Available online: [URL]: https://cancerstaging.org/references-tools/quickreferences/Cancer%20Staging%20Poster%20Picture%20Library/BreastPoster1.jpg
Grouping in stages
Stage 0: TisN0M0
Stage I: T1N0M0
Stage IIa: T0N1M0, T1N1M0, T2N0M0
Stage IIb: T2N1M0, T3N0M0
Stage IIIa: T0N2M0, T1N2M0, T2N2M0, T3N1M0, T3N2M0
Stage IIIb: T4N0M0, T4N1M0, T4N2M0
Stage IIIc: any TN3M0
Stade IV: any T and N, M1

[6] ECOG functional index: Eastern Cooperative Oncology Group Scale. Scale graded from 0 to 4 to define the patient's clinical status, i.e. functional capacity.

	- History of bone marrow or stem cell transplant. - Malignancy within the past 5 years, other than basal cell carcinoma, squamous cell carcinoma or cervical cancer. - Any disease or condition that the investigator feels could affect the patient's safety or the evaluation of the study criteria. - Pregnancy or breastfeeding
Treatment groups	The patients were randomised according to a 1:1 ratio to receive lipegfilgrastim 6 mg or pegfilgrastim 6 mg by subcutaneous injection on day 2 of each chemotherapy cycle.
Course of the study	- After randomisation, the patients received chemotherapy (doxorubicin 60 mg/m^2 and docetaxel 75 mg/m^2) on day 1 of each cycle. The chemotherapy was repeated every 3 weeks with a maximum of 4 cycles unless postponed due to an ANC or platelet count that was too low. A maximum period of 14 days was acceptable. - Lipegfilgrastim or pegfilgrastim was administered SC on day 2 of each cycle. - There was an end of study visit and 2 follow-up visits to test for any antibodies on day 180 and day 360 of the study.
Treatments given in combination	Chemotherapy (doxorubicin 60 mg/m^2 and docetaxel 75 mg/m^2) administered on day 1 of each cycle.
Primary efficacy endpoint	- Duration of severe neutropenia (DSN) in cycle 1. *Severe neutropenia* = grade 4 neutropenia with absolute neutrophil count (ANC) < 0.5 x 10^9/l *DSN* = Number of days following chemotherapy during which the ANC was < 0.5 x 10^9/l
Secondary endpoints included:	- Incidence of febrile neutropenia (FN) during cycles 1-4 of chemotherapy and overall impact of the FN on all 4 cycles of chemotherapy (investigator evaluation). - DSN during chemotherapy cycles 2, 3 and 4. During cycles 1, 2, 3 and 4: - Incidence of severe neutropenia. -Depth of nadir (the lowest count of neutrophils in the blood). - Time to onset of the nadir, defined as the time between the administration of chemotherapy and the onset of the nadir. - Time until normal neutrophil count: number of days between administration of the chemotherapy and reaching ANC ≥ 2 x 10^9/l during cycles 1 to 4. - Time until normal neutrophil count from reaching the nadir: number of days between the nadir and reaching ANC ≥ 1.5 x 10^9/l during cycles 1 to 4. - Proportion of patients who had reduced, non-administered or postponed chemotherapy doses. - Duration of hospitalisation (days) and stay in an intensive care unit related to treatment of FN or infections due to FN. - Quality of life, measured by the EORTC QLQ-C30 and QLQ-BR23 questionnaires (specific to breast cancer). These questionnaires were filled out by the patients a first time 24 hours after the start of cycle 1 and then a second time at the end of study visit.
Statistical analysis	Analysis on the per-protocol population: Due to the minimal difference sought, the least squares method and Poisson regression were used for the statistical analysis. The primary efficacy endpoint was analysed with a Poisson regression model, taking into account the treatment, country, type of chemotherapy (adjuvant/metastatic), and the weight class (≤ 60 kg, > 60 and ≤ 75 kg, > 75 kg), as fixed effects, and the ANC measured on day 1 of cycle 1 as the covariate. Lipegfilgrastim is considered non-inferior to pegfilgrastim in terms of DSN in cycle 1 if the upper limit of the 95% confidence interval of the difference in DSN between the two treatment groups was less than 1 day.

8.1.2 Results for the primary efficacy endpoint

A total of 202 patients were randomised (ITT population) according to a 1:1 ratio, i.e. 101 patients per treatment group.

The results were analysed in the PP population defined by randomised patients for whom no major protocol violation occurred during the study. The numbers in the PP population were as follows:
- pegfilgrastim group: n = 94
- lipegfilgrastim group: n = 94

The demographic characteristics were comparable between the ITT and PP populations, and also between the two treatment groups.
The patients had an average age of 51.1 in the pegfilgrastim group versus 49.9 in the lipegfilgrastim group. They were all women (100%). Their mean weight was 73.2 kg (pegfilgrastim) versus 73.9 kg (lipegfilgrastim).

Table 2: Characteristics and breast cancer evaluation in each treatment group

	pegfilgrastim 6 mg n (%)	**Lipegfilgrastim 6 mg** n (%)
Stage		
II at high risk	36 (35.6)	39 (38.6)
III	45 (44.6)	48 (47.5)
IV	20 (19.8)	14 (13.9)
ECOG functional index*		
0	47 (46.5)	45 (44.6)
1	54 (53.5)	56 (55.4)
2	0	0

* ECOG index:
0 = Fully active - The patient can carry out normal activity without any restriction
1 = Patient ambulatory, restricted in strenuous physical activity but may conduct an activity without major physical demands - light housework, office work.
2 = Patient ambulatory and able to take care of herself, but unable to work or do housework. In bed for less than 50% of the day.

Duration of severe neutropenia (DSN) in cycle 1:

Pegfilgrastim 6 mg n = 94	Lipegfilgrastim 6 mg n = 94	Difference in lipegfilgrastim 6 mg *versus* pegfilgrastim 6 mg		
mean DSN ± SD [days]		LSM	95% CI	p-value
0.8 ± 0.9	0.7 ± 0.9	-0.218	-0.498 to 0.062	0.1260

The non-inferiority of lipegfilgrastim vs pegfilgrastim was demonstrated on DSN during cycle 1: the upper limit of the confidence interval of the difference of DSN in cycle 1 between the two treatment groups (difference: -0.218, 95% CI = [-0.498; 0.062]) was below the predefined limit of non-inferiority (1 day).
The results of the ITT population were similar to those of the PP population.

Moreover, 51.1% of patients (48/94 patients) treated with pegfilgrastim and 43.6% of patients (41/94 patients) treated with lipegfilgrastim had severe neutropenia at cycle 1 of chemotherapy.

8.1.3 Results for the secondary efficacy endpoints:

The results were analysed in the PP population. The results observed in the ITT population were comparable for all the secondary endpoints.

Incidence of febrile neutropenia:
During the study: Three cases were described in the pegfilgrastim group (all in cycle 1) and no cases were counted in the lipegfilgrastim group.

DSN during cycles 2, 3 and 4:
No difference was observed between the pegfilgrastim and lipegfilgrastim groups in terms of DSN.
- during cycle 2 (difference: -0.123 (95% CI = [-0.282; 0.036]), NS
- during cycle 3 (difference: -0.029 (95% CI = [-0.145; 0.087]), NS
- during cycle 4 (difference: 0.008 (95% CI = [-0.147; 0.163]), NS

Incidence of severe neutropenia:

Cycle	Pegfilgrastim 6 mg			Lipegfilgrastim 6 mg			Lipegfilgrastim 6 mg *versus* pegfilgrastim 6 mg		
Incidence of severe neutropenia during cycles 1 to 4									
	N	n	%	N	n	%	Odds ratio	95% CI	p
1	94	48	51.1	94	41	43.6	0.745	0.405; 1.369	NS
2	93	20	21.5	94	8	8.5	0.291	0.110; 0.769	0.0130
3	91	11	12.1	93	8	8.6	0.676	0.249; 1.835	NS
4	91	11	12.1	90	11	12.2	0.997	0.391; 2.545	NS
All	94	55	58.5	94	47	50.0	0.708	0.383; 1.309	NS

Depth of the nadir and time to onset of the nadir during cycles 1 to 4

	Pegfilgrastim 6 mg		Lipegfilgrastim 6 mg		Lipegfilgrastim 6 mg *versus* pegfilgrastim 6 mg		
Depth of the nadir during cycles 1 to 4							
	N	Mean ± SD (10^9/l)	N	Mean ± SD (10^9/l)	LSM	95% CI	p
Cycle 1	94	1.0 ± 1.3	94	1.2 ± 1.3	0.189	-0.137; 0.515	NS
Cycle 2	94	2.0 ± 1.6	94	2.6 ± 2.1	0.659	0.110; 1.207	0.0189
Cycle 3	94	2.0 ± 1.5	94	2.5 ± 1.6	0.475	0.033; 0.917	0.0353
Cycle 4	94	2.3 ± 1.8	94	2.7 ± 1.7	0.404	-0.095; 0.904	NS

	Pegfilgrastim 6 mg		Lipegfilgrastim 6 mg		Lipegfilgrastim 6 mg *versus* pegfilgrastim 6 mg		
Time to onset of the nadir in cycle 1 to 4							
	N	mean ± SD [days]	N	mean ± SD [days]	LSM	95% CI	p
Cycle 1	94	7.0 ± 3.2	94	6.8 ± 3.6	-	-	-
Cycle 2	94	8.3 ± 4.4	94	8.5 ± 5.3	-	-	-
Cycle 3	94	8.5 ± 4.6	94	8.3 ± 4.8	-	-	-
Cycle 4	94	8.9 ± 5.3	94	10.0 ± 6.2	-	-	-

Time until normal neutrophil count: number of days between administration of the chemotherapy and reaching ANC ≥ 2 x 10^9/l during cycles 1 to 4

Cycle	Pegfilgrastim 6 mg		Lipegfilgrastim 6 mg		Lipegfilgrastim 6 mg *versus* pegfilgrastim 6 mg		
	N	mean ± SD [days]	N	mean ± SD [days]	LSM	95% CI	p
1	94	7.4 ± 3.6	94	5.9 ± 3.4	-1.589	-2.615; 0.563	0.0026
2	94	5.3 ± 4.6	94	3.6 ± 4.1	-1.661	-2.886; -0.436	0.0082
3	94	5.1 ± 4.3	94	3.9 ± 4.8	-1.344	-2.579; -0.108	0.0332
4	94	4.3 ± 4.7	94	3.3 ± 4.1	-0.802	-2.098; 0.493	NS

Proportion of patients who had reduced, non-administered or postponed chemotherapy doses

	Pegfilgrastim 6 mg			Lipegfilgrastim 6 mg		
Postponed administration of chemotherapy						
	N	n	%	N	n	%
Cycle 2	93	12	12.9	94	13	13.8
Cycle 3	91	17	18.7	93	14	15.1
Cycle 4	91	7	7.7	90	4	4.4

	Pegfilgrastim 6 mg			Lipegfilgrastim 6 mg		
Reduction of the chemotherapy dose or cancellation of chemotherapy						
	N	n	%	N	n	%
Cycle 2	93	4	4.3	94	0	0
Cycle 3	91	2	2.2	93	0	0
Cycle 4	91	2	2.2	90	0	0

Patient quality of life
Patient quality of life was determined by two questionnaires: EORTC QLQ-C30 and EORTC QLQ-BR23.
A reduction in patient quality of life was observed between these two visits in both treatment groups. There was no difference observed between the two treatment groups in the difference of quality of life rated between the start and the end of the study on both of these scales.

08.2 Adverse effects

The evaluation of the safety of lipegfilgrastim (LONQUEX) is mainly based on three studies: XM22-03 (presented above), a phase II pegfilgrastim-controlled, randomised, double-blind study (XM22-02-INT), and a phase III randomised, double-blind placebo-controlled study (XM22-04).
Patients included in XM22-04 received chemotherapy with cisplatin 80 mg/m^2 and etoposide 120 mg/m^2, in treatment of non-small cell lung cancer. This combination of chemotherapy has an 8 to 18% risk of febrile neutropenia,[7,8,9,10,11] and enabled the use of a placebo control group, as recommended by the EMA.[3] In return, this population does not correspond to the population defined in the European recommendations2,4 as requiring preventative treatment with G-CSF, this study could therefore not be considered in the assessment of the lipegfilgrastim efficacy data.
Lipegfilgrastim safety was assessed (EPAR, SPC) on the basis of the results of these three clinical studies, which included 503 patients (treated with lipegfilgrastim at different doses) and 76 healthy volunteers who received at least one dose of lipegfilgrastim.

8.2.1 Study XM22-03

The safety results were analysed in the ITT population.
The number of subjects in the ITT population was as follows:
- pegfilgrastim group: n = 101
- lipegfilgrastim group: n = 101

The percentage of adverse events was 98% (99/101) in the pegfilgrastim group and 99% (100/101) in the lipegfilgrastim group.
The percentage of treatment-related adverse events was 25.7% (26/101) in the pegfilgrastim group and 27.7% (28/101) in the lipegfilgrastim group.

[7] Bonomi P et al. Comparison of survival and quality of life in advanced non-small-cell lung cancer patients treated with two dose levels of paclitaxel combined with cisplatin versus etoposide with cisplatin: results of an Eastern Cooperative Oncology Group trial. J Clin Oncol 2000; 18: 623–31.
[8] Cardenal F et al. Randomized phase III study of gemcitabine-cisplatin versus etoposide-cisplatin in the treatment of locally advanced or metastatic non-small-cell lung cancer. J Clin Oncol 1999; 17: 12–8.
[9] Eckardt JR et al. Open-label, multicenter, randomized, phase III study comparing oral topotecan/cisplatin versus etoposide/cisplatin as treatment for chemotherapy-naive patients with extensive-disease small-cell lung cancer. J Clin Oncol 2006; 24: 2044–51.
[10] Hanna N et al. Randomized phase III trial comparing irinotecan/cisplatin with etoposide/cisplatin in patients with previously untreated extensive-stage disease small-cell lung cancer. J Clin Oncol 2006; 24: 2038–43.
[11] Mavroudis D et al. A multicenter randomized clinical trial comparing paclitaxel-cisplatin-etoposide versus cisplatin-etoposide as first-line treatment in patients with small-cell lung cancer. Ann Oncol 2001; 12: 463-70.

The most common treatment-related adverse events were:
- bone pain (9.9% (10/101) in the pegfilgrastim group versus 12.9% (13/101) in the lipegfilgrastim group).
- myalgia (5.0% (5/101) *vs.* 6.9% (7/101))
- erythema (3.0% (3/101) *vs.* 5.9% (6/101))
- arthralgia (0.0% *vs.* 3.0% (3/101))
- nausea (3.0% (3/101) *vs.* 2.0% (2/101)).

The percentage of treatment discontinuations for adverse events was 2% (2/101) in the pegfilgrastim group and 3% (3/101) in the lipegfilgrastim group.
The percentage of treatment discontinuations for treatment-related adverse events was 1% (1/101) with pegfilgrastim. No treatment discontinuations for treatment-related adverse events occurred in the lipegfilgrastim group.

Severe adverse events (grade 3-4) were reported in 34.7% of patients (35/101) in the pegfilgrastim group and in 25.7% of patients (26/101) in the lipegfilgrastim group. The main ones were: neutropenia (21.8% vs. 15.8%), alopecia (9.9% vs. 8.9%), leukopenia (3.0% vs. 5.0%), febrile neutropenia (3.0% vs. 1.0%), anaemia (1.0% vs. 2.0%).
Severe treatment-related adverse events (grades 3-4) were reported in 2 patients in the pegfilgrastim group (1 case of neutropenia and 1 case of paroxysmal tachycardia) and in 1 patient in the lipegfilgrastim group (1 case of epistaxis).

One death was reported during the study in the lipegfilgrastim group following grade 4 enterocolitis, this death was not attributed to the treatment. No deaths have been reported in the pegfilgrastim group.

8.2.2 Aggregated data from the three studies

According to the EPAR1 (P 92, 93, 95 and 103):
A total of 783 patients were randomised in the three studies, 503 patients were treated with lipegfilgrastim (including 399 with lipegfilgrastim at a dose of 6 mg), 155 with pegfilgrastim and 125 with placebo.
In placebo-controlled study XM22-04, mortality was higher in the short term (day 85) with lipegfilgrastim: 12.5% (31/248 patients) than with placebo: 7.2% (9/125 patients). These deaths were, most often, consecutive to the occurrence of an adverse event related to the disease (non-small cell lung cancer) or progression of the malignancy. At one year, mortality between the two groups was similar: 44% compared with 44.7%
This signal was not identified in XM22-03 (breast cancer). The literature (according to EPAR) reports the presence of G-CSF receptors on the surface of various tumour cells, therefore a hypothesis that G-CSF may accelerate the progression of the malignant process in some non-haematopoietic cancers, including non-small cell lung cancer, has been suggested. Uncertainty remains about the impact of this product or a class effect on the progression of the malignancy, therefore, the CHMP [Committee for Medicinal Products for Human Use] requested that a post-marketing clinical safety study be set up with the objective of providing an additional evaluation of the risk of disease progression and mortality associated with lipegfilgrastim in patients with malignant disease and treated with cytotoxic chemotherapy.

8.2.3 Immunogenicity

According to the SPC:
The anti-drug antibodies of 579 patients and healthy volunteers treated with lipegfilgrastim, 188 patients and healthy volunteers treated with pegfilgrastim and 121 patients treated with placebo were analysed. Drug-specific antibodies emerging after the start of treatment were detected in 0.86% of the subjects receiving lipegfilgrastim, in 1.06% of the subjects receiving

pegfilgrastim and in 1.65% of the subjects receiving placebo. No neutralising antibodies against lipegfilgrastim were observed.

Most biological medicinal products elicit some level of response by producing anti-drug antibodies. This antibody response can, in some cases, lead to undesirable effects or loss of efficacy. If a patient fails to respond to treatment, additional evaluations should be done.

08.3 Summary & discussion

In a comparative non-inferiority study versus pegfilgrastim (NEULASTA) in 202 patients with breast cancer of high-risk stage II, stage III or stage IV and treated with established cytotoxic chemotherapy, the non-inferiority of lipegfilgrastim was demonstrated compared with pegfilgrastim on the duration of severe neutropenia (DSN) in cycle 1 of chemotherapy: difference between the treatments: -0.218, (95% CI = [-0.498; 0.062]) or an upper limit of the confidence interval of less than 1 day, the predefined non-inferiority limit.
The main analysis was done on the PP population (94 patients in each treatment group).

The evaluation of lipegfilgrastim safety mainly relies on three studies: a phase II study (XM22-02-INT, n=208) and a phase III randomised, double-blind, pegfilgrastim-controlled study (XM22-03, n=202), and a phase III randomised, double-blind placebo-controlled study (XM22-04, n=373). The safety profile was evaluated on the ITT population in these studies.

In the randomised, double-blind study XM22-03, with lipegfilgrastim versus pegfilgrastim:
- The percentage of adverse events was 99% vs. 98% and that of treatment-related adverse events was 27.7% vs. 25.7%: these were most often musculoskeletal pain (bone pain, myalgia, arthralgia), rashes and nausea;
- the percentage of treatment discontinuations for adverse events was 3% (3/101) vs. 2% (2/101) and that of treatment-related adverse events was 0 vs. 1% (1/101);
- severe adverse events (grades 3-4) were reported in 25.7% of patients (26/101) vs. 34.7% (35/101), the main ones being: neutropenia (15.8% vs. 21.8 %), alopecia (8.9% vs. 9.9%), leukopenia (5.0% vs. 3.0%), febrile neutropenia (1.0% vs. 3.0%) and anaemia (2.0% vs. 1.0%);
- Severe treatment-related adverse events (grades 3-4) were reported in 1 patient in the lipegfilgrastim group (1 case of epistaxis) and 2 patients in the pegfilgrastim group (1 case of neutropenia and 1 case of paroxysmal tachycardia).

Mortality was higher with lipegfilgrastim: 12.5% (31/248 patients) than with placebo: 7.2% (9/125 patients), observed in the short term (day 85) in XM22-04 (non-small cell lung cancer), which is a pharmacovigilance signal: uncertainty remains about the impact of this product or a class effect on the progression of the malignancy. These deaths were, most often, consecutive to the occurrence of an adverse event related to the disease or progression of the malignancy. This signal was not identified in XM22-03 (breast cancer). Consequently, the CHMP asked that a post-marketing clinical safety study be set up.

08.4 Planned studies

The CHMP requested a post-marketing clinical safety study to provide an additional evaluation of the risks of disease progression and mortality associated with lipegfilgrastim in patients with a malignancy treated with cytotoxic chemotherapy.
The risks must be determined relative to pegfilgrastim and to a placebo and cancer progression must be evaluated objectively. A clinical model with adequate sensitivity must be selected to evaluate these risks. The submission of the final study report is expected by 30/06/2017.

A paediatric investigation plan is implemented to comply with the request by the EMA (EMEA-001019-PIP01-10 decision EMA P/112/2011 of 6 May 2011) through two studies (XM22-07 and XM22-08) in subjects aged 2-18 years with cancer and treated by

neutropenia-inducing chemotherapy. They aim to develop a paediatric presentation in a bottle allowing flexible dosage.
- XM22-07 (phase I): pharmacokinetics study;
- XM22-08 (phase III): efficacy study.
Safety and tolerance will be studied in both studies. The efficacy results will be extrapolated to the paediatric population below age 2 years.

Finally, LONQUEX is the subject of a risk management plan set up when its marketing authorisation was obtained.
Identified and potential risks of the RMP to be provided in the PSUR:
Identified risks
- Musculoskeletal pain:
- Allergic reactions
- Pulmonary adverse effects (interstitial pneumonia, ARDS)
- Thrombocytopenia
- Leukocytosis

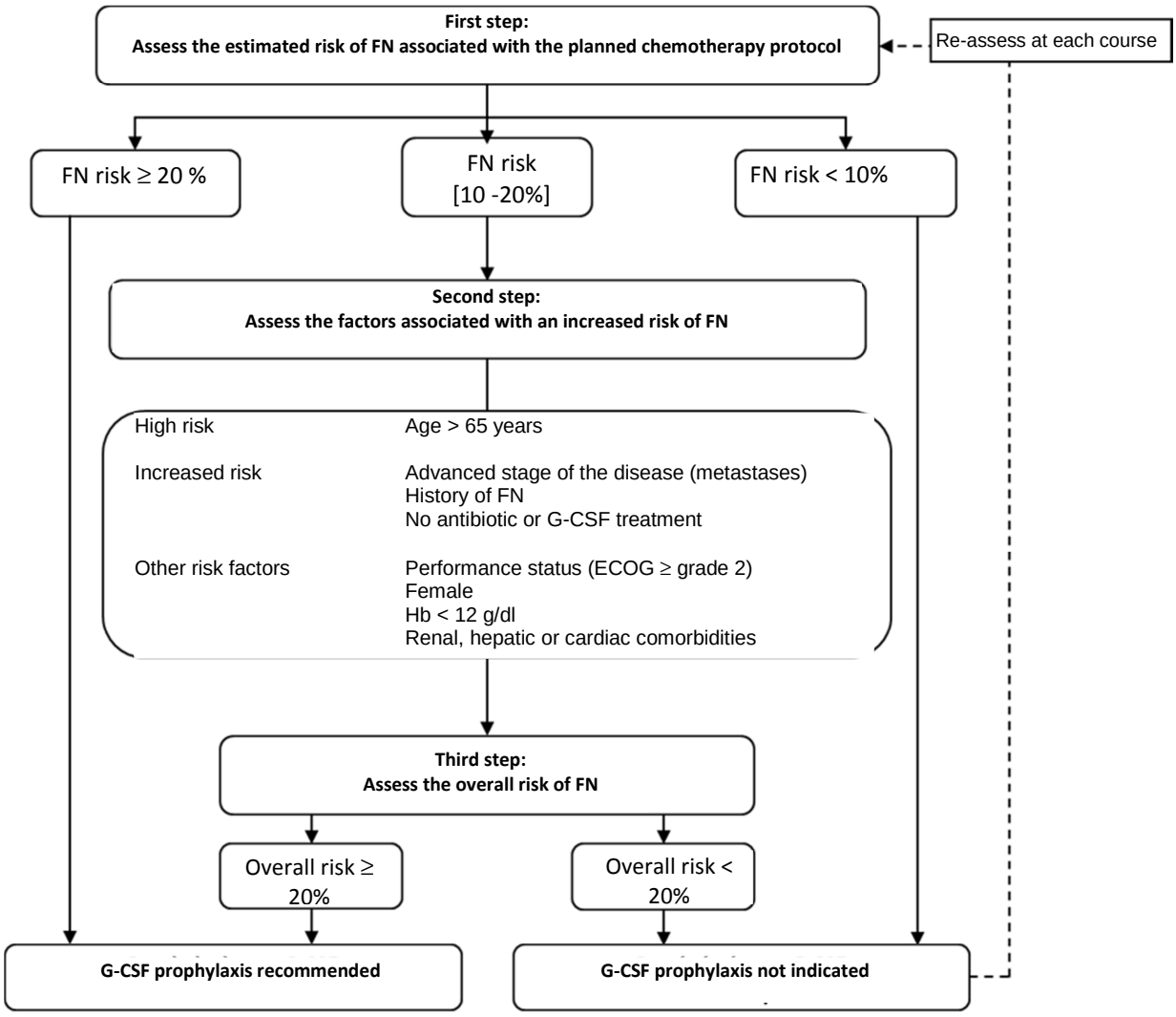
Potential risks
- Immunogenicity causing loss of efficacy. The immunogenicity data from paediatric studies XM22-07 and XM22-08 should also be provided.
- Sweet Syndrome
- Sickle cell crisis in patients with sickle cell disease
- Skin vascularity
- Splenomegaly/ruptured spleen
- Off-label use
- Overdose
- Progression of malignancy.

09 THERAPEUTIC USE

The use of colony stimulating factors (G-CSF) in oncology is recommended by the American Society of Clinical Oncology Practice (ASCO[12]), the European Society for Medical Oncology (ESMO[13]) and the European Organisation for Research and Treatment of Cancer (EORTC[2]) (Figure 1) in patients subjected to a protocol with a risk of febrile neutropenia greater than 20% or even 10% in some patients, in particular, above age 65, advanced stage of the disease, one or more prior episodes of febrile neutropenia, no antibiotic or G-CSF therapy, impaired nutritional status, cytopenia related to invasive spinal tumour, and extensive prior treatment(s), including wide area irradiation or combination chemotherapy.

[12] Smith Thomas J. and al. 2006 Update of Recommendations for the Use of White Blood Cell Growth Factors: An Evidence-Based Clinical Practice Guideline. ASCO 2006; 24, number 19
[13] Crawford J et al. Hematopoietic growth factors: ESMO Clinical Practice Guidelines for the applications. Ann Oncol 2010; 21(supplement 5): v248-v251

Figure 1: EORTC guidelines:



Source: Aapro MS et al. 2010 update of EORTC guidelines for the use of granulocyte-colony stimulating factor to reduce the incidence of chemotherapy-induced febrile neutropenia in adult patients with lymphomas and solid tumours. Eur J Cancer (2011) 47: 8-32.

Due to the lack of benefit in terms of efficacy and the risk of excess premature mortality in its use in non-small cell lung cancer, the long-acting granulocyte colony stimulating factor lipegfilgrastim (LONQUEX) cannot be considered as an alternative to pegfilgrastim (NEULASTA) in first-line treatment in primary* and secondary** prevention of chemotherapy-induced febrile neutropenia in adult patients treated with cytotoxic chemotherapy for malignancy (with the exception of chronic myeloid leukaemia and myelodysplastic syndromes). The role of this proprietary medicinal product in the current therapeutic strategy cannot be defined.

* Administration of G-CSF, before the occurrence of neutropenia, in cycle 1 and the subsequent cycles.

** Administration of G-CSF if a neutropenia episode was observed in the prior cycle, then administration in the subsequent cycles.

The medicinal use of colony stimulating factors should be limited solely, according to the EORTC,2 to patients with chemotherapy-induced neutropenia, who do not respond to appropriate antibiotic therapy and who develop life-threatening infectious complications (such as severe sepsis or septic shock).

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

◗ Febrile neutropenia is life threatening due to the infectious complications that it can cause.

◗ It is intended as a prophylactic and curative therapy.

◗ No advantage in terms of efficacy has been demonstrated (non-inferiority versus NEULASTA) for this proprietary medicinal product. A short-term excess mortality risk has been evidenced in the use in patients with non-small cell lung cancer.

◗ There are treatment alternatives to this proprietary medicinal product, represented by another long-acting G-CSF, pegfilgrastim (NEULASTA) and several short-acting G-CSFs, filgrastim (NEUPOGEN, NIVESTIM, RATIOGRASTIM, TEVAGRASTIM, ZARZIO) and lenograstim (GRANOCYTE).

◗ Given the lack of advantage in terms of efficacy relative to its comparator (pegfilgrastim) and a short-term excess mortality risk in use in patients with non-small cell lung cancer, this proprietary medicinal product has no role in the therapeutic strategy.

◗ Public health benefit: It is not expected that LONQUEX will benefit public health given the existing treatment alternatives and the absence of additional impact on public health criteria (reduction of mortality, improved quality of life) relative to the current prevention of chemotherapy-induced neutropenia.

Taking account of these points, (non-inferiority only demonstrated in terms of efficacy, uncertainty with regard to the risk of early death in non-small cell lung cancer, the existence of alternative medicinal products), the Transparency Committee considers that the actual benefit of LONQUEX <u>is insufficient</u> to justify reimbursement by National Health Insurance.

011 TRANSPARENCY COMMITTEE RECOMMENDATIONS

The Committee does not recommend inclusion on the list of medicines refundable by National Health Insurance or on the list of medicines approved for hospital use in the indication "Reduction in the duration of neutropenia and the incidence of febrile neutropenia in adult patients treated with cytotoxic chemotherapy for malignancy (with the exception of chronic myeloid leukaemia and myelodysplastic syndromes)" and at the dosages in the Marketing Authorisation.