HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

Opinion

2 April 2014

HERCEPTIN 600 mg/5 ml, solution for injection

6 ml vial (CIP: 34009 585 576 9 9)

Applicant: ROCHE SAS

INN	Trastuzumab
ATC code (2013)	L01XC03 (Monoclonal antibodies – Antineoplastic agents)
Reason for the request	**Inclusion**
List concerned	**Inclusion for hospital use** (French Public Health Code L.5123-2)
Indications concerned	**"-<u>Metastatic breast cancer:</u>** **HERCEPTIN is indicated for the treatment of adult patients with HER2 positive metastatic breast cancer (MBC):** **- as monotherapy for the treatment of those patients who have received at least two chemotherapy regimens for their metastatic disease. Prior chemotherapy must have included at least an anthracycline and a taxane unless patients are unsuitable for these treatments. Hormone receptor positive patients must also have failed hormonal therapy, unless patients are unsuitable for these treatments;** **- in combination with paclitaxel for the treatment of those patients who have not received chemotherapy for their metastatic disease and for whom an anthracycline is not suitable;** **- in combination with docetaxel for the treatment of those patients who have not received chemotherapy for their metastatic disease;** **- in combination with an aromatase inhibitor for the treatment of postmenopausal patients with hormone-receptor positive MBC, not previously treated with trastuzumab.**

	- <u>Early breast cancer:</u> **HERCEPTIN is indicated for the treatment of adult patients with HER2 positive early breast cancer (EBC):** **- following surgery, chemotherapy (neoadjuvant or adjuvant) and radiotherapy (if applicable);** **- following adjuvant chemotherapy with doxorubicin and cyclophosphamide, in combination with paclitaxel or docetaxel;** **- in combination with adjuvant chemotherapy consisting of docetaxel and carboplatin;** **- in combination with neoadjuvant chemotherapy followed by adjuvant HERCEPTIN therapy, for locally advanced (including inflammatory) disease or tumours > 2 cm in diameter.** **HERCEPTIN should only be used in patients with metastatic or early breast cancer whose tumours have either HER2 overexpression or HER2 gene amplification as determined by an accurate and validated assay."**

Actual Benefit	**The actual benefit of subcutaneous (SC) HERCEPTIN is substantial.**
Improvement in Actual Benefit	**The new subcutaneous formulation of HERCEPTIN is an addition to the range, complementing the intravenous formulation of HERCEPTIN that is currently available.** **Consequently, subcutaneous HERCEPTIN does not provide any improvement in actual benefit (level V, non-existent) compared with intravenous HERCEPTIN.**
Therapeutic use	**The new subcutaneous formulation of HERCEPTIN is an addition to the range, complementing the intravenous formulation of HERCEPTIN.** **The subcutaneous formulation of HERCEPTIN has only been studied in early breast cancer and its role in the therapeutic strategy for this condition is the same as intravenous HERCEPTIN. In other cases, its use as a straightforward alternative to the intravenous formulation has not been assessed.**
Recommendations	**The Committee notes that, as with the intravenous formulation, patients should be observed for six hours after the first injection of subcutaneous HERCEPTIN and for two hours after subsequent injections for signs or symptoms of administration-related reactions, as stated in the SPC (Administration-related reactions, Pulmonary events).**

01 ADMINISTRATIVE AND REGULATORY INFORMATION

Marketing Authorisation (procedure)	26 August 2013 (centralised procedure)
Prescribing and dispensing conditions / special status	List I Medicine for hospital prescription only. Prescription restricted to oncology specialists or physicians with cancer training. Medicinal product requiring special monitoring during treatment. Initial administration must be carried out in a hospital environment.

ATC Classification	2013	
	L	Antineoplastic and immunomodulating agents
	L01	Antineoplastic agents
	L01X	Other antineoplastic agents
	L01XC	Monoclonal antibodies
	L01XC03	trastuzumab

02 BACKGROUND

Inclusion of a new pharmaceutical form (subcutaneous, SC) and new dosage (600 mg) of HERCEPTIN (trastuzumab), an addition to the range complementing the proprietary medicinal product HERCEPTIN 150 mg, powder for concentrate for solution for intravenous (IV) infusion, available since 2000.

HERCEPTIN 600 mg/5 ml, solution for subcutaneous injection obtained centralised Marketing Authorisation on 26 August 2013 in all the breast cancer indications already granted for the IV form of HERCEPTIN.
To date, unlike the IV form, SC HERCEPTIN does not have Marketing Authorisation for the treatment of gastric cancer.

03 THERAPEUTIC INDICATIONS

The new subcutaneous formulation of HERCEPTIN, an addition to the range complementing the intravenous formulation, has identical indications to IV HERCEPTIN in **breast cancer**.

- **Metastatic breast cancer:**

"HERCEPTIN is indicated for the treatment of adult patients with HER2 positive metastatic breast cancer (MBC):

- as monotherapy for the treatment of those patients who have received at least two chemotherapy regimens for their metastatic disease. Prior chemotherapy must have included at least an anthracycline and a taxane unless patients are unsuitable for these treatments. Hormone receptor positive patients must also have failed hormonal therapy, unless patients are unsuitable for these treatments;

- in combination with paclitaxel for the treatment of those patients who have not received chemotherapy for their metastatic disease and for whom an anthracycline is not suitable;

- in combination with docetaxel for the treatment of those patients who have not received chemotherapy for their metastatic disease;

in combination with an aromatase inhibitor for the treatment of postmenopausal patients with hormone-receptor positive MBC, not previously treated with trastuzumab."

- **Early breast cancer:**

"HERCEPTIN is indicated for the treatment of adult patients with HER2 positive early breast cancer (EBC):

- following surgery, chemotherapy (neoadjuvant or adjuvant) and radiotherapy (if applicable);

- following adjuvant chemotherapy with doxorubicin and cyclophosphamide, in combination with paclitaxel or docetaxel;

- in combination with adjuvant chemotherapy consisting of docetaxel and carboplatin;

- in combination with neoadjuvant chemotherapy followed by adjuvant HERCEPTIN therapy, for locally advanced (including inflammatory) disease or tumours > 2 cm in diameter.

HERCEPTIN should only be used in patients with metastatic or early breast cancer whose tumours have either HER2 overexpression or HER2 gene amplification as determined by an accurate and validated assay (see SPC)."

The application for registration of the subcutaneous form of HERCEPTIN, unlike the IV form, did not concern gastric cancer; therefore, the proprietary medicinal product SC HERCEPTIN is not indicated in gastric cancer.

04 DOSAGE

"HER2 testing is mandatory prior to initiation of therapy. HERCEPTIN treatment should only be initiated by a physician experienced in the administration of cytotoxic chemotherapy, and should be administered by a healthcare professional only.

It is important to check the product labels to ensure that the correct formulation (intravenous or subcutaneous fixed dose) is being administered to the patient, as prescribed.

HERCEPTIN subcutaneous formulation is not intended for intravenous administration and should be administered via a subcutaneous injection only.
Limited information is currently available on switches from one formulation to the other.

Posology
The recommended dose for HERCEPTIN subcutaneous formulation is 600 mg/5 ml irrespective of the patient's body weight. No loading dose is required. This dose should be administered subcutaneously over 2-5 minutes every three weeks.

In the pivotal trial (BO22227) HERCEPTIN subcutaneous formulation was administered in the neoadjuvant/adjuvant setting in patients with early breast cancer. The preoperative chemotherapy regimen consisted of docetaxel (75 mg/m²) followed by FEC (5FU, epirubicin and cyclophosphamide) at a standard dose."

Treatment duration:
Patients with MBC should be treated with HERCEPTIN until progression of disease.
Patients with EBC should be treated with HERCEPTIN for 1 year or until disease recurrence, whichever occurs first.

Dose reduction:
No reductions in the dose of HERCEPTIN were made during clinical trials. Patients may continue therapy during periods of reversible, chemotherapy-induced myelosuppression but they should be monitored carefully for complications of neutropenia during this time. Refer to the Summary of

Product Characteristics (SPC) for paclitaxel, docetaxel or aromatase inhibitor for information on dose reduction or delays.

If left ventricular ejection fraction (LVEF) drops ≥ 10 ejection fraction (EF) points from baseline AND to below 50%, treatment should be suspended and a repeat LVEF assessment performed within approximately 3 weeks. If LVEF has not improved, or declined further, or symptomatic congestive heart failure (CHF) has developed, discontinuation of HERCEPTIN should be strongly considered, unless the benefits for the individual patient are deemed to outweigh the risks. All such patients should be referred for assessment by a cardiologist and followed up.

Special populations:
Dedicated pharmacokinetic studies in older people and those with renal or hepatic impairment have not been carried out. In a population pharmacokinetic analysis, age and renal impairment were not shown to affect trastuzumab disposition.

Paediatric population:
There is no relevant use of HERCEPTIN in the paediatric population.

Missed doses:
If the patient misses a dose of HERCEPTIN subcutaneous formulation, it is recommended to administer the next 600 mg dose (i.e. the missed dose) as soon as possible. The interval between consecutive HERCEPTIN subcutaneous formulation administrations should not be less than three weeks.

Method of administration:
The 600 mg dose should be administered as a subcutaneous injection only, over 2-5 minutes.
The injection site should be alternated between the left and right thigh. New injections should be given at least 2.5 cm from the old site and never into areas where the skin is red, bruised, tender, or hard. During the treatment course with HERCEPTIN subcutaneous formulation, other medicinal products for subcutaneous administration should preferably be injected at different sites.

Patients should be observed for six hours after the first injection and for two hours after subsequent injections for signs or symptoms of administration-related reactions."

05 THERAPEUTIC NEED

In France, breast cancer is the most common female cancer, with an estimated 48,800 new cases in 2012.[1] It accounts for 31.5% of all new cases of cancer in women and almost 14% of all incident cancers in both sexes. It is a serious and life-threatening disease, particularly when the patient presents with metastases. With almost 11,900 estimated deaths in 2012, breast cancer is the leading cause of cancer deaths in women[1] (less than 1% of breast cancers affect men).

In breast cancer, overexpression of the HER2 receptor (human epidermal growth factor receptor 2) and/or HER2 gene amplification are factors indicating a poorer prognosis than HER2 negative breast cancer.[2] Almost 15% of patients newly diagnosed at an early stage are HER2 positive[3,4]and this is close to 30% for patients diagnosed at an advanced stage.[5] The incidence of HER2 positive breast cancer at any stage is thus estimated to be between 7700 and 10,000 cases per year.

During the last 10 years, the availability of HERCEPTIN in HER2 overexpressing breast cancer indications has prolonged the overall survival of patients with metastatic breast cancer and increased survival rates in patients with breast cancer diagnosed at an early stage (early breast cancer) who receive neoadjuvant and adjuvant therapy.

Intraveinous formulation of HERCEPTIN has been available since 2001, as a powder for concentrate for infusion which is reconstituted with water for injections. IV HERCEPTIN dosage is adjusted to the patient's weight and requires the administration of a initial loading dose (8 mg/kg or 4 mg/kg depending on the treatment regimen) as a 90-minute infusion, followed, if the loading dose was well tolerated, with maintenance doses (6 mg/kg every 3 weeks or 2 mg/kg every week depending on the treatment regimen) as a 30-minute infusion.

SC HERCEPTIN, an addition to the IV HERCEPTIN range, is a new ready-to-use formulation allowing 5 ml trastuzumab to be administered subcutaneously, corresponding to a fixed dose of 600 mg, without a loading dose, whatever the patient's weight.

[1]Les cancers en France en 2013. Collection of status reports and knowledge updates, collective work published by INCa [National Cancer Institute], Boulogne-Billancourt, January 2014.
[2]Dawood S, Broglio K, Ensor J, et al. Survival differences among women with de novo stage IV and relapsed breast cancer. Ann Oncol 2010; 21:2169-2174.
[3]Wolff AC, Hammond ME, Schwartz JN, et al. American Society of Clinical Oncology / College of American Pathologists guideline recommendations for human epidermal growth factor receptor 2 testing in breast cancer. Arch. Pathol. Lab. Med. 2007; 131(1):18-43.
[4]INCa. Les tests de génétique moléculaire pour l'accès aux thérapies ciblées. Collection of reports and summaries, collective work. Boulogne-Billancourt. December 2011.
[5]Press MF, Slamon DJ, Flom KJ, et al. Evaluation of HER2/neu gene amplification and overexpression: comparison of frequently used assay methods in a molecularly characterized cohort of breast cancer specimens. J. Clin. Oncol. 2002; 20(14):3095-3105.

06 CLINICALLY RELEVANT COMPARATORS

06.1 Medicinal products

As SC HERCEPTIN is an addition to the range, the only clinically relevant comparator is IV HERCEPTIN (see Table 1) in all HER2 positive breast cancer indications (early and metastatic breast cancer).

Table 1: Summary of previous Committee assessments of IV HERCEPTIN in its breast cancer indications

INN	Indication	Date of TC opinion	AB	IAB
IV HERCEPTIN trastuzumab	Treatment of HER2+ metastatic breast cancer: - as **monotherapy** **- in combination with paclitaxel**	28/03/2001	Substantial	-
		20/07/2005	Substantial	II in combination. Not allocated as monotherapy.
	Treatment of HER2+ metastatic breast cancer: - in **combination with docetaxel**	20/07/2005	Substantial	II
	Adjuvant treatment of HER2+ breast cancer, following surgery, chemotherapy (neoadjuvant or adjuvant) and radiotherapy (if applicable)	04/10/2006	Substantial	I
	Treatment of HER2+ metastatic breast cancer: - in **combination with an aromatase inhibitor**	19/03/2008	Substantial	V
	Treatment of HER2+ early breast cancer: - **in combination with neoadjuvant chemotherapy** followed by adjuvant HERCEPTIN® therapy, in patients with locally advanced (including inflammatory) disease or tumours > 2 cm in diameter	09/01/2013	Substantial	Not currently evaluable

06.2 Other health technologies

N/A

Conclusion

HERCEPTIN (trastuzumab) for intravenous injection is the clinically relevant comparator.

07 INTERNATIONAL INFORMATION ON THE MEDICINAL PRODUCT

The subcutaneous form of HERCEPTIN is currently reimbursed in a number of European countries.

Country	REIMBURSEMENT	
	YES/NO	Population: MA population or restricted
European Union		
Austria	Yes	
Germany	Yes	
Denmark	Yes	
Italy	In progress	
Spain	In progress	Marketing Authorisation
Finland	Yes	
Great Britain	Yes	
Netherlands	Yes	
Portugal	Yes	
Sweden	Yes	
USA	No – no MA application submitted	
Canada	No – MA application withdrawn	
Switzerland	No – MA application withdrawn	
Japan	No – no MA application submitted	
Chile	In progress	Available since 09/10/2013 in the private sector in the indication HER2+ early breast cancer

08 ANALYSIS OF AVAILABLE DATA

In support of its application, the company submitted results from a phase III trial evaluating the non-inferiority of the SC form to the IV form (follow-up still ongoing, study due to end in 2017).
To date, the long-term follow-up phase of the HannaH study is still ongoing and two analyses will be performed: the first when all patients will have completed 2 years of follow-up after finishing treatment, and the second at 60 months of follow-up.

The efficacy, safety and pharmacokinetic profile of the new SC form of trastuzumab (HERCEPTIN) have thus been examined in a phase III trial (the HannaH study)[6] evaluating the non-inferiority of SC HERCEPTIN to the IV form.

The fixed dose of 600 mg HERCEPTIN administered subcutaneously every 3 weeks was determined in a phase I/Ib dose-finding and dose-confirmation study (BP22023)[7] through a pharmacokinetic simulation model.
The BP22023 dose-finding study confirmed that a dose of 8 mg/kg SC HERCEPTIN obtained trough serum concentrations (C_{min}) of trastuzumab equivalent to those observed with a 6 mg/kg infusion of IV HERCEPTIN (corresponding to the IV trastuzumab maintenance dose approved for treatment of HER2+ breast cancer).

[6]Ismael G, Hegg R, Muehlbauer S, *et al.* Subcutaneous *versus* intravenous administration of (neo)adjuvant trastuzumab in patients with HER2-positive, clinical stage I-III breast cancer (HannaH study): a phase 3, open-label, multicentre, randomised trial. Lancet Oncol. 2012;13:869-78
[7]Wynne C, Vernon H, Schwabe C, *et al*. Comparison of Subcutaneous and Intravenous Administration of Trastuzumab: A Phase I/Ib Trial in Healthy Male Volunteers and Patients With HER2-Positive Breast Cancer. J Clin Pharmacol. 2012; 53:192-201.

The pharmacokinetic simulation model determined that a SC fixed dose of 600 mg trastuzumab (independent of the patient's weight) administered every 3 weeks:

- had equivalent pharmacokinetics (C_{min} at cycle 8 pre-dose) to a weight-adjusted dose of IV trastuzumab (8 mg/kg loading dose then maintenance doses of 6 mg/kg every 3 weeks);
- obtained a trough concentration (C_{min}) > 20 µg/ml, at which HER2 receptor saturation is complete, ensuring the antitumour efficacy of trastuzumab;
- did not require a loading dose.

08.1 Efficacy

8.1.1 Phase III trial: HannaH (BO22227)[6]

This study aimed to evaluate the pharmacokinetics, efficacy and safety of SC trastuzumab compared with IV trastuzumab in patients with early breast cancer overexpressing HER2, in an adjuvant and neoadjuvant setting.

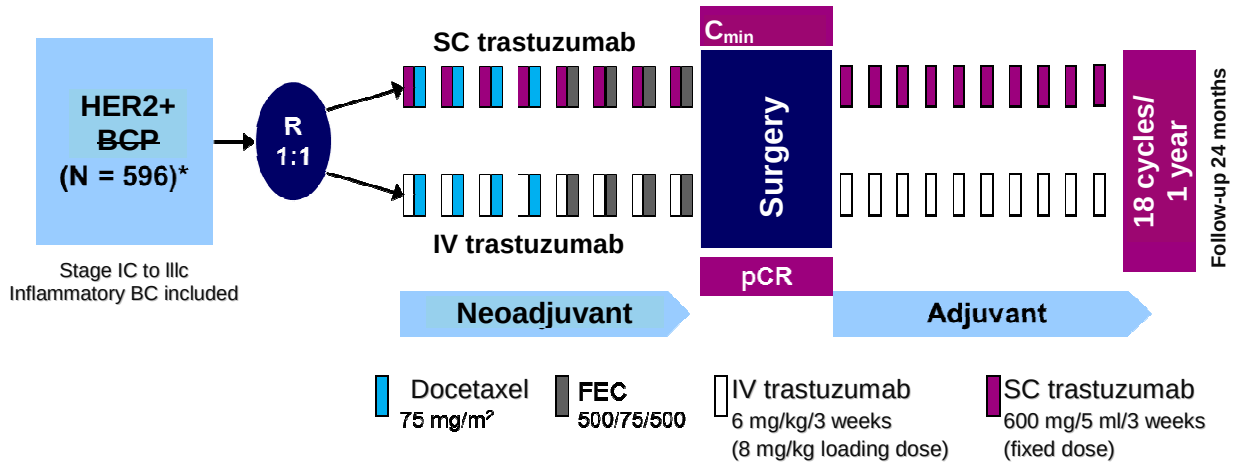
No clinical efficacy and safety data are available for subcutaneously administered HERCEPTIN in patients with metastatic cancer.
The co-primary endpoints allow the two forms of HERCEPTIN, SC and IV, to be compared only in a neoadjuvant setting (before surgery).

Type of study	International comparative, randomised, open-label, phase III non-inferiority trial
Date and duration of study	Enrolment: 19/10/2009 to 01/12/2010 Patient follow-up: until 24 months after completing adjuvant treatment with SC or IV trastuzumab, or until progression (whichever occurs first).
Study objective	To demonstrate the **non-inferiority** of the SC form of HERCEPTIN to the IV form in terms of pharmacokinetics (C_{min} at cycle 8 pre-dose) and pathological complete response (pCR*) after eight cycles of treatment, in a neoadjuvant and adjuvant setting. ** no invasive tumour cells in the breast, as demonstrated by microscopic examination of the surgical specimen by pathologists at the study site.*
METHOD	
Selection criteria	**Inclusion criteria:** Women ≥ 18 years of age Primary tumour of the breast stage I (T1N0M0) to III (TnN3M0) including inflammatory and multicentric/multifocal forms: tumour size ≥ 1 cm ~~by~~ ultrasound or ≥ 2 cm ~~by~~ palpation, histologically confirmed, HER2 positive with overexpression confirmed centrally At least 1 measurable lesion in breast or lymph nodes (size ≥ 1 cm on ultrasound or ≥ 2 cm on palpation), except for T4d inflammatory cancer ECOG 0 or 1 LVEF at inclusion ≥ 55 %
Study size and sites	84 sites in 24 countries (5 sites in France with 28 patients)
Products studied	Patients randomised into two groups (open-label): - **SC trastuzumab:** 600 mg every 3 weeks - **IV trastuzumab:** loading dose of 8 mg/kg then maintenance dose of 6 mg/kg every 3 weeks During the **neoadjuvant** period, in combination with SC or IV trastuzumab, all patients received preoperative chemotherapy consisting of four cycles of docetaxel (75 mg/m²) every 3 weeks followed by four cycles of the FEC protocol (5-FU [500 mg/m²] + epirubicin

	[75 mg/m²] + cyclophosphamide [500 mg/m²]) every 3 weeks, i.e. eight cycles. **After surgery** scheduled following the eight cycles of chemotherapy + SC or IV trastuzumab, patients continued to receive trastuzumab as adjuvant monotherapy, administered as per their randomisation group, for the last 10 cycles. The total number of trastuzumab cycles was therefore 18 cycles, i.e. 1 year of treatment. Patients were followed up until 24 months after finishing SC or IV trastuzumab, as adjuvant therapy, or until progression, whichever occurred first **(see Figure 1)**.
Co-primary efficacy endpoints	- **Pharmacokinetic endpoint:** C_{min} at cycle 8 pre-dose (i.e. before surgery) - **Clinical endpoint:** pCR after eight cycles of neoadjuvant therapy
Secondary endpoints	Event-free survival, overall survival, time to response, overall response rate, safety, immunogenicity, pharmacokinetic profile, total pathological complete response
Sample size	A sample of 130 patients was necessary to demonstrate non-inferiority for the PK endpoint (difference between SC trastuzumab C_{min} and IV trastuzumab C_{min}) with a statistical power of 80%. A sample of 552 patients was necessary to demonstrate non-inferiority for the clinical endpoint (pCR) with a statistical 80% power . **Randomisation:** 596 patients (299 in the IV group and 297 in the SC group)
Randomisation method	Block randomisation (ratio 1:1), stratified on the following criteria: - disease stage: immediately operable versus locally advanced versus inflammatory - oestrogen receptor status: positive versus negative versus unknown
Method of analysing the results	- **Primary pharmacokinetic endpoint:** SC trastuzumab was established as non-inferior if the lower limit of the 90% confidence interval (90% CI) for the geometric mean Ctrough ratio (SC C_{min}/IV C_{min}) was ≥ 0.8 (per-protocol population analysis). - **Primary clinical endpoint:** SC trastuzumab was established as non-inferior if the lower limit of the 97.5% confidence interval (97.5% CI) for the difference in pathological complete response (SC pCR - IV pCR) was > -12.5% (per-protocol analysis).
RESULTS	
Number of subjects analysed	The results submitted come from **two analyses**: - **12/07/2011:** 1st analysis in the per-protocol population: Final analysis of both co-primary endpoints (C_{min} before surgery and pCR on the surgical specimen) performed when 116 patients had completed adjuvant therapy with trastuzumab. For the pharmacokinetic endpoint (C_{min}), the analysis was carried out in 469 patients (234 in the SC group and 235 in the IV group). For the clinical endpoint (pCR), the analysis was carried out in 523 patients (260 in the SC group and 263 in the IV group), corresponding to the per-protocol population. The ITT population, used for a sensitivity analysis of the clinical efficacy endpoint, consisted of 591 patients (294 in the SC group and 297 in the IV group). - **09/07/2012:** 2nd analysis of the secondary endpoints (safety, overall survival, and event-free survival).
Duration of follow-up	- **1st analysis:** The median duration of patient follow-up was 12 months (12.4 months in the SC trastuzumab group versus 12.2 months in the IV trastuzumab group). - **2nd analysis:** The median duration of patient follow-up was 20 months (20.4 [0.3; 31.9] months in the SC trastuzumab group versus 19.7 months [1.0; 31.3] in the IV trastuzumab group).
Patient characteristics and comparability between groups	Baseline patient characteristics were comparable in both groups in terms of demographics and pathology; about 45% of patients had stage T2 HER2+ breast cancer, LVEF was 66%, and mean age was 50 years.
Primary endpoint results	- **Primary pharmacokinetic endpoint (C_{min}):** The geometric mean Ctrough ratio (SC C_{min}/IV C_{min}) was 1.33 (90% CI: [1.24; 1.44]). As the lower limit of the confidence interval was 1.24,

	the pharmacokinetic non-inferiority of the SC trastuzumab group to the IV trastuzumab group was demonstrated. Subgroup analyses of the C_{min} showed that patients' weight had no impact on the results, confirming that a single dose of SC trastuzumab is appropriate. - **Primary clinical endpoint (pCR):** The pathological complete response rate was 45.4%, 95% CI [39.2%; 51.7%] in patients in the SC trastuzumab group versus 40.7%, 95% CI [34.7%; 46.9%] in patients in the IV trastuzumab group, with an absolute difference (SC pCR - IV pCR) of 4.7 points in favour of the SC trastuzumab group. As the lower limit of the 97.5% CI for the difference in pathological complete response between the two groups was -4, the non-inferiority of the SC trastuzumab group to the IV trastuzumab group was demonstrated in terms of efficacy as measured by pCR.
Secondary endpoint results	- **Secondary pharmacokinetic endpoints:** The majority of patients (≥ 97%) obtained a C_{min} > 20 µg/ml, the minimum value at which trastuzumab is effective. - **Secondary efficacy endpoints:** At the 1st analysis, the event-free survival and overall survival data were not mature: only 13/260 patients (5.0%) in the SC trastuzumab group and 15/263 patients (5.7%) in the IV trastuzumab group had reported an event of any kind (disease recurrence, disease progression [local, regional, distant or contralateral] or death from any cause). At the 2nd analysis, patients' event-free survival and overall survival were as follows: the majority of patients (85%) had no events (disease recurrence or local, regional, distant or contralateral progression of the disease); 19 patients (7 patients in the SC group and 12 in the IV group) had died. The EFS and OS results were therefore still immature at this stage, and they will be available at the end of the follow-up period. The EFS and OS data in the ITT population were consistent with those in the primary analysis (per-protocol population).

Figure 1: Design of the HannaH study



SC: subcutaneous; IV: intravenous; BCP: breast cancer patients; C_{min}: trough concentration; BC: breast cancer; FEC: 5-FU, epirubicin and cyclophosphamide chemotherapy protocol; pCR: pathological complete response.

08.2 Safety

8.2.1 Safety - Phase III trial: HannaH (BO22227)

The HannaH study safety data come from the second analysis (09/07/2012).
The safety population was defined as all patients with at least one dose of the study treatment (SC or IV trastuzumab) during at least one of the treatment phases (neoadjuvant, adjuvant or follow-up phase).

The safety population included 595 patients (one patient did not receive trastuzumab due to a major deviation from the protocol):

- 297 patients in the SC trastuzumab group
- 298 patients in the IV trastuzumab group

The populations in both groups were comparable in terms of duration of exposure to trastuzumab and to chemotherapy.

A comparable percentage of patients with at least one adverse event (AE) was reported in both treatment groups (see Table 2):

- 97.6% of patients (290/297) in the SC trastuzumab group
- 94.6% of patients (282/298) in the IV trastuzumab group

More hypertensive AEs were reported in the SC trastuzumab group (9.8% [29/297]) than in the IV trastuzumab group (4.7% [14/298]), and there were more severe or serious postoperative wound infections in the SC trastuzumab group (3.0% [9/297]) than in the IV trastuzumab group (1.7% [5/298]).
In both groups, the most common AEs (> 25% in each group) were alopecia, nausea, neutropenia, diarrhoea and asthenia.

The majority of AEs were reported during the combined trastuzumab and cytotoxic chemotherapy phase.

The incidence of serious adverse events (SAEs) was lower in the IV group than in the SC group (see Table 2):

- 21.5% (64/297) in the SC trastuzumab group
- 14.1% (42/298) in the IV trastuzumab group

The most commonly reported SAEs (≥ 2 %) were infections (24/297; 8.1% in the SC group and 13/298; 4.4% in the IV group) and haematological toxicity (21/297; 7.1% in the SC group and 20/298; 6.7% in the IV group). Neutropenia (febrile or non-febrile) was the most common haematological SAE in both treatment groups. In addition, a small number of cardiac disorders were reported more frequently in the SC trastuzumab group (5/297; 1.7%) than in the IV trastuzumab group (2/298; 0.7%).

This difference in incidence for serious AEs was not found for severe AEs (grades 3-5):

- 53.5% (159/297) in the SC trastuzumab group
- 52.3% (156/298) in the IV trastuzumab group

Table 2: Safety data from the HannaH study

	IV HERCEPTIN (n=298)	SC HERCEPTIN (n=297)
No. of patients with ≥ 1 AE (any grade)	282 (94.6%)	290 (97.6%)
No. of patients with ≥ 1 serious AE	42 (14.1%)	64 (21.5%)
No. of patients with ≥ 1 severe AE (grade 3-5)	156 (52.3%)	159 (53.5%)

The incidence of treatment discontinuation due to AEs was 5.7% (17/297) in the SC trastuzumab group versus 2.7% (8/298) in the IV trastuzumab group.

Six AEs, including four during the neoadjuvant phase, led to the patient's death:
- 1.3% (4/297) in the SC trastuzumab group
- 0.7% (2/298) in the IV trastuzumab group

Two of these deaths (septic shock, myocardial infarction), both in the SC group only, were deemed to be treatment-related by the investigators.
The mortality rate was comparable in both treatment groups:
- 5.1% (15/297) in the SC trastuzumab group
- 6.0% (18/298) in the IV trastuzumab group

Administration-related reactions (of any grade) were more common in the subcutaneous treatment group than in the intravenous treatment group:
- 47.8% (142/297) in the SC trastuzumab group
- 37.2% (111/298) in the IV trastuzumab group

The cardiac disorders reported for the subcutaneous formulation were comparable with those known to be associated with the IV formulation. The cardiac AE profile was comparable between both treatment groups, although there were more grade ≥ 3 cardiac AEs in the SC group (1.7%; 5/297) than in the IV group (1%; 3/298).

The duration of SC trastuzumab administration in the study was 2.96 minutes (0;12) which is less than the theoretical duration of administration of about 5 minutes.
These subcutaneous injections were generally well tolerated (there were injection site reactions in 11.1% of patients [33/297]). Most events were mild in severity (grade 1). Only five events were grade 2.

8.2.2 Immunogenicity - Phase III trial: HannaH (BO22227)

Immunogenicity was examined in the HannaH study as a secondary endpoint.
Samples for the evaluation of immunogenicity (anti-drug antibodies [ADAs] and neutralising antibodies) were evaluated at baseline, on D1 of cycles 2, 5 (pre-surgery), 13 and 18 (post-surgery), and 3, 6, 12, 18 and 24 months after the last dose of trastuzumab.

Anti-trastuzumab antibodies:

	Patients	**Anti-trastuzumab antibodies present**	**Patients**	**Anti-trastuzumab antibodies present** ***(Neutralising antibodies)***
	Inclusion		**Date of 2nd analysis (09/07/2012)**	
SC HERCEPTIN group N (%)	290	16 (5.5%)	295	43 (14.6%) *(4)*
IV HERCEPTIN group N (%)	291	18 (6.2%)	296	21 (7.1%) *(2)*

At baseline, 290 patients in the SC trastuzumab group and 291 patients in the IV trastuzumab group were evaluable for immunogenicity (seven patients in each treatment group did not have an available sample for the immunogenicity evaluation).
At baseline, 5.5% of patients in the SC trastuzumab group (16/290) versus 6.2% of patients in the IV trastuzumab group (18/291) had anti-trastuzumab antibodies.
At 2nd analysis time, samples for immunogenicity evaluation were not available for four patients (two in each group) after inclusion 295 patients in the SC trastuzumab group and 296 in the IV trastuzumab group were evaluable for immunogenicity

In total, 14.6% of patients in the SC trastuzumab group (43/295) versus 7.1% of patients in the IV trastuzumab group (21/296) had anti-trastuzumab antibodies.

Four patients in the SC trastuzumab group versus two patients in the IV trastuzumab group had developed neutralising antibodies.

Anti-rHuPH20 antibodies (a new excipient present in the SC form)

	Patients	Anti-rHuPH20 antibodies present	Patients	Anti-rHuPH20 antibodies present *(Neutralising antibodies)*
	Inclusion		Date of 2nd analysis (09/07/2012)	
SC HERCEPTIN group N (%)	290	22 (7.6%)	295	48 (16.3%) *(0)*
IV HERCEPTIN group N (%)	291	Not applicable	296	Not applicable

At baseline, samples for immunogenicity evaluation were not available before treatment with SC trastuzumab, in seven patients. 290 patients in the SC trastuzumab group were evaluable for immunogenicity at baseline.
At baseline, 7.6% of patients (22/290) in the SC trastuzumab group had anti-rHuPH20 antibodies.

On 9 July 2012, samples for immunogenicity evaluation were not available in two patients after inclusion. 295 patients in the SC trastuzumab group were evaluable for immunogenicity.

In total, 16.3% of patients (48/295) in the SC trastuzumab group had anti-rHuPH20 antibodies.
No patient developed neutralising antibodies to rHuPH20.

The clinical consequences of anti-rHuPH20 antibodies are not known. However, the pharmacokinetics, efficacy (as determined by pathological complete response [pCR]) and safety of SC and IV trastuzumab seem to be not affected by the presence of these antibodies.

Longer-term follow-up data are necessary to evaluate the immunogenicity profile of SC versus IV trastuzumab.

8.2.3 Risk management plan (RMP)

In its updated March 2013 version, the RMP identifies the following risks for HERCEPTIN: cardiac dysfunction, administration-related reactions, haematological toxicity, oligohydramnios and respiratory disorders.
With the new formulation, the potential risks are: infections, risk of confusion between the IV and SC forms, immunogenicity/hypersensitivity and anaphylaxis from the SC form, and the short-term relative safety of the higher absolute dose intensity of the subcutaneous formulation compared with the IV formulation.
Missing information was identified as: treatment of male patients, the long-term relative safety of the higher absolute dose intensity of the SC formulation compared with the IV formulation, and the safety of 75 mg/m^2 doses of docetaxel versus 100 mg/m^2. As part of this risk management plan, the EMA has asked the pharmaceutical company to carry out annual comparisons of combinations of SC trastuzumab with docetaxel 75 mg/m² or 100 mg/m², to monitor whether, in practice, higher doses of docetaxel than those administered in the clinical trial above would lead to an increase in SC trastuzumab toxicity.

In addition to routine pharmacovigilance, some risks are subject to specific guided questionnaires (used when documenting cases reported by health professionals), namely cardiac function, administration-related reactions, haematological toxicity, pulmonary function and the risk of confusion between the IV and SC formulations. Cardiac function (multi-gated acquisition scan) will be followed up in patients in the HannaH study until 5 years after treatment has finished.

Immunogenicity and hypersensitivity and anaphylactic reactions with the SC formulation will also be monitored.
Safety when treating male patients and the safety of 75 mg/m^2 versus 100 mg/m^2 docetaxel doses will be subject to specific analyses, respectively in each PSUR (periodic safety update report) and annually.

In addition to the different sections in the SPC and patient information leaflet, risk minimisation actions have been proposed for some risks:

- cardiac dysfunction: a treatment algorithm for reduced ventricular ejection fraction
- HER2 receptor overexpression: a website about the HER2 test for anatomical pathologists

Following the RMP assessment, version No. 11.2, the PRAC (Pharmacovigilance Risk Assessment Committee) requested a phase IV clinical trial to evaluate the safety of SC HERCEPTIN in metastatic breast cancer, in particular with appropriate cardiac monitoring.

08.3 Summary & discussion

In the HannaH phase III pivotal study the pharmacokinetic profile of the subcutaneous HERCEPTIN formulation was comparable to the intravenous formulation. In the neoadjuvant and adjuvant setting, the two formulations were non-inferior.

8.3.1 Efficacy

The efficacy of the subcutaneous form of trastuzumab (HERCEPTIN 600 mg/5 ml) was evaluated in a non-inferiority study versus the intravenous form of trastuzumab (HERCEPTIN 150 mg). The HannaH phase III non-inferiority study included 596 women with HER2+ early breast cancer.
The non-inferiority of SC trastuzumab to the IV form was demonstrated in terms of pharmacokinetic response (C_{min}) and pathological complete response (pCR):

- The geometric mean Ctrough ratio (SC C_{min}/IV C_{min}) was 1.33 (90% CI: [1.24; 1.44]); the lower limit of the confidence interval was 1.24, i.e. greater than 0.8, the minimum value for demonstrating the non-inferiority of the SC trastuzumab group to the IV trastuzumab group; the majority of patients (≥ 97%) obtained a C_{min} > 20 µg/ml, the minimum value at which trastuzumab is effective.
- The new subcutaneous formulation of HERCEPTIN reached a pCR (pathological complete response: no invasive tumour cells in the breast) that was non-inferior to the intravenous form: pCR was 45.4% with the SC form versus 40.7% with the IV form (95% CI: [-4.0; 13.4]); the lower limit of the confidence interval was -4, i.e. greater than -12.5, the minimum value for demonstrating the non-inferiority of the SC trastuzumab group to the IV trastuzumab group.

These results also confirmed that a subcutaneous fixed dose of 600 mg trastuzumab every 3 weeks is appropriate whatever the patient's weight (subgroup analysis).
Efficacy was demonstrated through a comparison of pCR rates in patients with HER2+ early breast cancer in the adjuvant/neoadjuvant setting, and no data is currently available for metastatic patients. However, extrapolation of these efficacy data to the metastatic population was considered acceptable by the EMA.[6]

8.3.2 Safety

No new safety signals were identified during clinical trials. The overall safety of SC trastuzumab was comparable to IV trastuzumab in terms of the nature and incidence of events reported.
The immunogenicity data were consistent with previous experience with the IV form and no new signals were detected regarding the new excipient in the subcutaneous form (rHuPH20). The

immunogenicity of SC trastuzumab did not have any impact on the efficacy and safety of treatment in the available clinical trial.

Adverse events were equally distributed between the two formulations of trastuzumab: 97.6% (290/297 patients) for the subcutaneous formulation versus 94.6% (282/298 patients) for the intravenous formulation.
The majority of adverse events were reported during the neoadjuvant phase, when trastuzumab was combined with a cytotoxic chemotherapy protocol.
The cardiac disorders reported for the SC formulation of trastuzumab were comparable to those known to be associated with the IV formulation.

The imbalance observed in serious adverse events, namely 21.5% (64/297) with the SC formulation versus 14.1% (42/298) with the IV formulation, was not detected for severe adverse events (grade ≥ 3): 53.5% (159/297) with the SC formulation versus 52.3% (156/298) with the IV formulation. The authors of the CHMP [Committee for Medicinal Products for Human Use] report[6] could not conclude that there was any difference in safety between the two formulations (SC and IV).

Administration-related reactions (ARRs) (of any grade) were more common in the subcutaneous treatment group (47.8%, 142/297) than in the intravenous treatment group (37.2%, 111/298).
According to the SPC for the proprietary medicinal product SC HERCEPTIN (section 4.4: Special warnings and precautions for use), “Although serious ARRs, including dyspnoea, hypotension, wheezing, bronchospasm, tachycardia, reduced oxygen saturation and respiratory distress, were not reported in the clinical trial with the HERCEPTIN subcutaneous formulation, caution should be exercised as these have been associated with the intravenous formulation. Patients should be observed for ARRs for six hours after the first injection and for two hours after subsequent injections.”
As regards pulmonary events, according to the SPC, “Caution is necessary with HERCEPTIN subcutaneous formulation as severe pulmonary events have been reported with the use of the intravenous formulation in the post-marketing setting. These events have occasionally been fatal and may occur as part of an infusion-related reaction or with delayed onset. In addition, cases of interstitial lung disease including lung infiltrates, acute respiratory distress syndrome, pneumonia, pneumonitis, pleural effusion, respiratory distress, acute pulmonary oedema and respiratory insufficiency have been reported.”

Long-term safety data (from the follow-up phase of the HannaH study) will be necessary to evaluate the long-term immunogenicity (anti-rHuPH20 antibodies) and safety profiles of this new pharmaceutical form of HERCEPTIN.

08.4 Planned studies

The clinical development plan for SC HERCEPTIN is still in progress, particularly through the HannaH study (BO22227) with its follow-up phase still ongoing. An analysis of event-free survival and overall survival (secondary endpoints) will be carried out from the end of the 24-month follow-up period for all patients.

In addition, the pharmaceutical company indicates that it hopes to market subcutaneous HERCEPTIN in the form of a single-use injection device (SID) soon.
The development plan submitted by the company is as follows:

- Phase I study BO25532 (completed) demonstrating the comparability of $AUC_{0\rightarrow 21\ days}$ and C_{max} values for SC trastuzumab administered either via a SID or using a syringe with a hypodermic needle
- Phase II PerfHer study (ongoing) evaluating patient and healthcare professional preference for SC administration (vial or SID) in comparison with IV administration

In addition, two phase IV trials are under way:

- SafeHer study (international and non-comparative): a safety/tolerability follow-up study
- Metaspher study (French and comparative): a study evaluating whether metastatic patients responding to first-line treatment with IV trastuzumab for at least 3 months prefer SC or IV administration; the safety and tolerability of SC trastuzumab; healthcare professionals' experience in and preference for each route of administration; and patients' quality of life.

09 THERAPEUTIC USE

According to its Marketing Authorisation wording, HERCEPTIN (trastuzumab) may be used in the treatment of HER2-positive early breast cancer (in a neoadjuvant or adjuvant setting) as well as in metastatic patients.
Its therapeutic use in breast cancer varies depending on the cancer stage (early or metastatic).
According to national and international guidelines for the treatment of HER2 positive early[8,9,10] and metastatic[11,12] breast cancer, HERCEPTIN is currently the standard treatment recommended for the management of HER2 positive breast cancer at any stage of the disease.

HER2+ early breast cancer:
According to the 2010 HAS guide on the management of breast cancer, a neoadjuvant systemic treatment (before surgery) may be considered in cases of infiltrating and sizeable and/or inflammatory cancer, and in cancers that are immediately inoperable. Thus, neoadjuvant treatment is a medical practice that comes within the scope of adjuvant therapy.
International and national good clinical practice guidelines recommend neoadjuvant chemotherapy (with anthracyclines and taxanes[13]) in patients with early breast cancer and advise that trastuzumab should be added from the neoadjuvant phase of treatment (before surgery) in patients with HER2 positive breast cancer.
Adjuvant therapy is indicated in patients with localised breast cancer with or without lymph node involvement (N+ or N-) but with a significant risk of recurrence (>10% at 10 years). This consists of chemotherapy combined if necessary with radiotherapy. For patients with a hormone-receptor-positive tumour, adjuvant hormone therapy is also indicated.
HER2 status should be established at the time of initial disease diagnosis to determine the therapeutic strategy for early treatment and consider whether HERCEPTIN (in the absence of contraindications, particularly cardiac contraindications) should be used in addition to cytotoxic chemotherapy.

HER2+ metastatic breast cancer:
The main objective in metastatic patients is to prolong survival and reduce the size of the tumour and metastases so as to ease symptoms while maintaining the most acceptable quality of life possible. If the tumour overexpresses the HER2 receptor, the European[11] and international[12] good practice guidelines recommend a HERCEPTIN-based treatment, in combination with chemotherapy and/or hormone therapy, as first-line therapy for metastatic disease.

[8]Aebi S, Davidson T, Gruber G, *et al*. Primary breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2011; 22 (Suppl 6):vi12-vi24.
[9]NCCN. Clinical Practice Guidelines in Oncology. Breast Cancer. Version 2.2011.
[10]Ceugnart L, Coudert B, Dalenc F, *et al*. Les traitements néoadjuvants (hors cancer du sein inflammatoire) -RPC Nice Saint-Paul de Vence 2011. Oncologie 2011; 13: 658-680.
[11]Cardoso F, Harbeck N, Fallowfield L, et al. Locally recurrent or metastatic breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2012; 23 Suppl 7):vii11–vii19.
[12]Cardoso F, Costa A, Norton L, et al. 1st International consensus guidelines for advanced breast cancer (ABC 1). Breast 2012; 21:242-52.
[13]Goldhirsch A, Wood WC, Coates AS, *et al*. Strategies for subtypes--dealing with the diversity of breast cancer: highlights of the St. Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2011. Ann Oncol 2011; 22:1736-47.

First-line systemic pharmacological treatment with chemotherapy and/or hormone therapy is recommended in the therapeutic management of metastatic-stage breast cancer.[14] The treatment is selected based primarily on:

- the histological characteristics of the tumour
- factors predicting response to treatment (hormone receptor and/or HER2 receptor expression)
- prognostic factors
- previous treatments taken by the patient and how these were tolerated
- time interval between (neo)adjuvant therapy and first-line metastatic treatment
- type of metastases (number of sites, size and localisation)
- the patient's general health.

In tumours overexpressing the HER2 receptor, the recommended 1st-line treatment is trastuzumab combined with a taxane (paclitaxel or docetaxel) irrespective of hormone status.
The combination of pertuzumab (PERJETA), trastuzumab and docetaxel has proven progression-free survival benefits and is therefore a new first-line therapy for HER2+ metastatic breast cancer. The American NCCN guidelines[15] consider that adding pertuzumab to dual therapy with trastuzumab and a taxane is preferable to dual therapy alone.
However, no data are currently available to assess the combination of pertuzumab and trastuzumab (HERCEPTIN) administered subcutaneously.

The subcutaneous form of HERCEPTIN is a new therapeutic option for managing patients with HER2+ breast cancer who are eligible for HERCEPTIN treatment.
It has been shown to be non-inferior to the intravenous form of trastuzumab.
The SC formulation of HERCEPTIN has only been studied in early breast cancer and its role in the therapeutic strategy for this condition is the same as IV HERCEPTIN. In other cases, its use as a straightforward alternative to the intravenous formulation has not been assessed.

In practice, as adjuvant monotherapy or as maintenance treatment for metastatic cancer, this subcutaneous formulation could lead to greater convenience of use (shorter duration of administration, less invasive route of administration, less time-consuming to prepare). When HERCEPTIN is administered (subcutaneously or intravenously), patients should be observed for six hours after the first injection and for two hours after subsequent injections for signs or symptoms of administration-related reactions.

Limited information is currently available on switching from one formulation (SC or IV) to the other (see SPC).

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

◗Breast cancer is a serious and life-threatening disease.
◗This proprietary medicinal product is intended as specific curative cancer therapy.
◗The efficacy/adverse effects ratio for the new subcutaneous formulation of HERCEPTIN is comparable to the intravenous formulation: this efficacy/adverse effects ratio is high.

[14]INCa – HAS – Chronic Condition Guide – Breast Cancer - January 2010.
[15]National Comprehensive Cancer Network Breast cancer (NCCN 2013)
http://www.nccn.org/professionals/physician_gls/pdf/breast.pdf.

◗There is a treatment alternative: intravenous HERCEPTIN.
◗This is a first-line therapy for HER2 positive breast cancers.

◗Public health benefit:
In France, the public health burden of breast cancer is substantial (939,297 DALYs, Euro zone A, 2004 estimate). The population eligible for treatment of HER2 positive early or metastatic breast cancer with subcutaneous HERCEPTIN is smaller, and the public health burden of the disease at this stage is moderate.
Improving the management quality of cancer patients and their quality of life is a public health need which is an established priority (objective 49 of the Law of 9 August 2004 on public health policy, Cancer Plan 2014-2019, Plan to improve the quality of life of patients with chronic diseases 2007-2011).
However, taking into account the results of studies, demonstrating the non-inferiority of subcutaneous HERCEPTIN to the intravenous form, it is not expected that subcutaneous HERCEPTIN will have any additional impact on patients' morbidity and quality of life.
The availability of the subcutaneously administered form could have an impact on the organisation of the healthcare system, by allowing the duration of administration of the treatment to be reduced to 2 to 5 minutes instead of 90 minutes for the first course and 2 to 5 minutes instead of 30 minutes for subsequent courses. However, patients must still be monitored after administration.
Consequently, taking into account the other treatments available, it is not expected that SC HERCEPTIN will have any additional impact on public health, in comparison with the intravenous form, in these indications.

Consequently, the Committee considers that the actual benefit of HERCEPTIN 600 mg/5 ml, solution for injection is substantial in the Marketing Authorisation indications.

The Committee recommends inclusion of HERCEPTIN 600 mg/5 ml, solution for injection on the list of medicines approved for hospital use in the indications and at the dosages in the Marketing Authorisation.

010.2 Improvement in actual benefit (IAB)

The new subcutaneous formulation of HERCEPTIN is an addition to the range, complementing the intravenous formulation of HERCEPTIN that is currently available.
Consequently, subcutaneous HERCEPTIN does not provide any improvement in actual benefit (level V, non-existent) compared with intravenous HERCEPTIN.

010.3 Target population

The target population for the new subcutaneous formulation of HERCEPTIN is identical to that of IV HERCEPTIN in all its breast cancer indications. This population includes:

- patients with HER2+ early breast cancer receiving adjuvant therapy;
- patients with HER2+ early breast cancer receiving neoadjuvant therapy; this population is included in the previous population;
- patients with HER2+ metastatic breast cancer. This population can be divided into two subpopulations:
  - patients first diagnosed at metastatic stage;
  - patients with recurrence after an adjuvant treatment (metastatic or local and unresectable recurrence).

HER2+ early breast cancer

- Adjuvant

The incidence of breast cancer in France was estimated at 48,763 new cases in 2012.[16]
About 95%[17]of patients are diagnosed at the early stage of the disease, corresponding to an annual figure of 46,325 patients.
Overexpression of HER2 affects 11.76% of patients with breast cancer diagnosed at an early stage in France,[17] i.e. about 5448 patients diagnosed in the early stages of the disease in 2012.
The target population for HERCEPTIN as adjuvant therapy for breast cancer is estimated at about 6000 cases per year.

- Neoadjuvant

The target population for HERCEPTIN used in this setting (as neoadjuvant followed by adjuvant therapy) was recently estimated by the Transparency Committee[18] as between 735 and 1712 patients per year, a population already included in HERCEPTIN's indication as adjuvant therapy for HER2 positive breast cancer.

HER2+ metastatic breast cancer in any line of therapy

- *Patients diagnosed with metastatic disease from the outset:*

The incidence of breast cancer in women in France was estimated at 48,763 cases in 2012.[19]
The proportion of breast cancers first diagnosed at metastatic stage is estimated to be 5% of all diagnosed cases, i.e. about 2440 patients per year.
Overexpression of HER2 affects 28% to 30% of patients with breast cancer diagnosed at an advanced stage in France[19] **i.e. between 680 and 730 patients first diagnosed at metastatic stage in 2012.**

- *Patients who relapsed after adjuvant treatment and have progressed to a metastatic stage*

The company submitted a model with a time horizon of 10 years (the probability of recurrence beyond that period being regarded as zero), incorporating, for each year, data on the incidence of breast cancer,[23] the proportion of breast cancers diagnosed early (estimated at 95% of all cases diagnosed),[17] the proportion among these of HER2 positive breast cancers (estimated at 11.76% of breast cancers diagnosed early),[25] and the proportion among these of breast cancers that recurred after adjuvant treatment in 2012 (estimated from retrospective data from cohorts of patients treated with[20] or without[21] trastuzumab during management of their primary tumour).

According to this model, about 1195 patients had a recurrence in 2012 in France.
In addition, no data are available that could be used for a precise estimate of the proportions of patients with metastatic or local and unresectable recurrence.
The target population for HERCEPTIN in metastatic disease could be estimated at **about 2000 patients per year**, including 730 patients first diagnosed at the metastatic stage and 1200 patients with recurrence after an adjuvant treatment (metastatic or local and unresectable recurrence).
The total target population for SC HERCEPTIN can be estimated at about 8000 patients per year.

[16]INCa, January 2014: Les cancers en France, édition 2013.
[17]INCa. Survie attendue des patients atteints de cancers en France : état des lieux. Reports and summaries, collective work. Boulogne-Billancourt. April 2010.
[18]HERCEPTIN, Transparency Committee (HAS) opinion of 9 January 2013
[19] Kantar Health. Baromètre réalisé sur 253 patientes atteintes de cancer du sein métastatique HER2 positif actuellement traitées par Trastuzumab / chimiothérapie (hors essais cliniques), dont 149 en 1ère ligne. June 2011.
[20]Romond EH, Perez EA, Bryant J, *et al*. Trastuzumab plus adjuvant chemotherapy for operable HER2-positive breast cancer. N Engl J Med 2005;353:1673-84.
[21]Paik S, Bryant J, Tan-Chiu E, *et al*. HER2 and choice of adjuvant chemotherapy for invasive breast cancer: National Surgical Adjuvant Breast and Bowel Project Protocol B-15. J Nat Cancer Inst 2000;92:1991-8.

Packaging:
Appropriate for the prescribing conditions as regards indication, dosage and treatment duration.

Other requests
The Committee wishes to reiterate that, as with the intravenous formulation, patients should be observed for six hours after the first injection of subcutaneous HERCEPTIN and for two hours after subsequent injections for signs or symptoms of administration-related reactions, as stated in the SPC (Administration-related reactions, Pulmonary events).