HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

Opinion

14 May 2014

STIVARGA 40 mg, film-coated tablet

B/28 (CIP: 3400927520006)

Applicant: BAYER SANTE

INN	regorafenib
ATC code (2012)	L01XE21 (protein kinase inhibitors)
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	**"STIVARGA is indicated for the treatment of adult patients with metastatic colorectal cancer (CRC) who have been previously treated with, or are not considered candidates for available therapies, in particular fluoropyrimidine-based chemotherapy, an anti-VEGF therapy and an anti-EGFR therapy."**

Actual Benefit	**In the treatment of metastatic colorectal cancer previously treated with or not considered suitable for available therapies, in particular fluoropyrimidine-based chemotherapy, an anti-VEGF therapy and an anti-EGFR therapy, the actual benefit of STIVARGA:** **- is low for patients whose performance score is 0-1** **- is insufficient for patients whose performance score is > 1**
Improvement in Actual Benefit	**Given the safety profile and the poor level of effect, the Committee considers that STIVARGA does not provide any improvement in actual benefit (level V, non-existent) in the treatment of metastatic colorectal cancer patients who failed on or were not considered candidates for available therapies (fluoropyrimidine-based chemotherapy, an anti-VEGF therapy and an anti-EGFR therapy) and whose performance score is 0 or 1.**
Therapeutic use	**Given the modest activity at the cost of significant toxicity, STIVARGA may only be proposed for patients previously treated with all available therapies. In addition, as there is no data for patients with an ECOG score > 1, STIVARGA should only be proposed for patients with a performance score of 0-1.**

01 ADMINISTRATIVE AND REGULATORY INFORMATION

Marketing Authorisation	Date initially granted: 26 August 2013 (European centralised procedure) Temporary authorisation for use by a cohort [ATU de cohort in French] prior to Marketing Authorisation in this indication, on 29 November 2012
Prescribing and dispensing conditions/special status	List I Medicine for hospital prescription Medicine requiring special monitoring during treatment. Prescription restricted to cancer treatment or clinical oncology specialists and departments.

ATC Classification	2013	
	L	Antineoplastic and immunomodulating agents
	L01	Antineoplastic agents
	L01X	Other antineoplastic agents
	L01XE	Protein kinase inhibitors
	L01XE21	regorafenib

02 BACKGROUND

This is a review of the request for the inclusion of the proprietary medicinal product STIVARGA 40 mg, film-coated tablet, on the list of medicines refundable by National Health Insurance and the list of medicines approved for hospital use.

Regorafenib is an oral tumour deactivation agent that significantly inhibits multiple protein kinases, including those involved in tumour angiogenesis (VEGFR1, 2, 3 and TIE2), oncogenesis (KIT, RET, RAF-1, BRAF and BRAFV600E) and the tumour micro-environment (PDGFR and FGFR).

03 THERAPEUTIC INDICATIONS

"STIVARGA is indicated for the treatment of adult patients with metastatic colorectal cancer (CRC) who have been previously treated with, or are not considered candidates for available therapies, in particular fluoropyrimidine-based chemotherapy, an anti-VEGF therapy and an anti-EGFR therapy."

04 DOSAGE

"STIVARGA should be prescribed by physicians experienced in the administration of anticancer therapy.
Dosage

The recommended dose of regorafenib is 160 mg (4 tablets of 40 mg) taken once daily for 3 weeks followed by 1 week off therapy. This 4-week period is considered a treatment cycle.
If a dose is missed, then it should be taken on the same day as soon as the patient remembers. The patient should not take two doses on the same day to make up for a missed dose. In case of vomiting after regorafenib administration, the patient should not take additional tablets.
Treatment should continue as long as benefit is observed or until unacceptable toxicity occurs (see section 4.4 of the SPC).
Patients with performance status (PS) 2 or higher were excluded from clinical studies. There is limited data in patients with PS ≥2."

05 THERAPEUTIC NEED

World-wide, colorectal cancer is the third most common cancer in men and the second most common among women.
The stage of the cancer at the time of diagnosis is the most relevant factor regarding prognosis. The survival rate at five years ranges from 93% for a stage I disease to less than 10% for stage IV (metastatic). In approximately 60% of cases, initial diagnosis is made during the latter stages of the disease and the prognosis and median survival without treatment is around six months.
Currently, there are no approved treatments available for metastatic colorectal cancer patients who have had failed treatments with fluoropyrimidine-, oxaliplatin- or irinotecan-based therapies or targeted therapies available.

06 CLINICALLY RELEVANT COMPARATORS

STIVARGA is indicated for metastatic colorectal cancer after failure or progression with all approved therapies. At this stage of the disease, patients are treated with supportive care or included in treatment studies.
Therefore, there are no clinically relevant comparators available.

◗ Conclusion

There are no clinically relevant comparators available for this stage of the disease.

07 INTERNATIONAL INFORMATION ON THE MEDICINAL PRODUCT

Country	Date of MA	Status	Indications
Switzerland	27.02.13	Reimbursed up to May 2015	MA indication
United States	27.09.12	Marketed	STIVARGA is a protein kinase inhibitor indicated in the treatment of metastatic colorectal cancer in patients previously treated with fluoropyrimidines, oxaliplatin, irinotecan, anti-VEGF therapy and, if they have the non-mutated KRAS gene, with anti-EGFR therapy. “STIVARGA is a kinase inhibitor indicated for the treatment of patients with metastatic colorectal cancer (CRC) who have been previously treated with fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy, an anti-VEGF therapy, and, if KRAS wild type, an anti-EGFR therapy.”
Canada	11.03.13	Under assessment	STIVARGA (regorafenib) is indicated in the treatment of metastatic colorectal cancer (CRC) patients who have previously received fluoropyrimidine-, oxaliplatin- or irinotecan-based chemotherapy and anti-VEGF therapy, and, for those with the wild type KRAS gene (or non-mutated), anti-EGFR therapy.
Japan	25.03.13	Marketed	Advanced or recurrent, unresectable colorectal cancer.

08 ANALYSIS OF AVAILABLE DATA

The dossier submitted includes a phase III pivotal study (CORRECT study or study 14387) which evaluated the therapeutic benefit of regorafenib (STIVARGA) in the treatment of metastatic colorectal cancer.

08.1 Efficacy

CORRECT Study

Comparative, randomised (2:1), double-blind, placebo-controlled study on metastatic colorectal cancer patients who have had disease progression after receiving all lines of standard recommended treatments.

The primary efficacy endpoint was overall survival, defined as the time between randomisation and the death of the patient from any cause.

Secondary efficacy endpoints were:
- Progression-free survival, defined as the period (in days) between randomisation and the date of progression of the disease (observed clinically or radiologically) or death from any cause.
- The objective response rate, defined as the percentage of patients whose best overall response is either complete response, or partial repose according to RECIST version 1.1 criteria. Patients for whom their best overall response was not a complete or partial response, and all patients who did not have an evaluation after the start of treatment were considered as non-responders for the analysis.
- The overall management of the disease rate, defined as the percentage of patients with a complete or partial response or a stable disease.

The tumours were measured at inclusion and every eight weeks during the treatment period to evaluate progression-free survival, the overall response and management of the disease. They were evaluated up to disease progression, defined radiologically or clinically, according to RECIST criteria.

The main inclusion criteria were as follows:
- patients aged at least 18 years
- stage IV (metastatic) colorectal cancer
- documented adenocarcinoma of the colon or the rectum (through histology or cytology). All other histological types were excluded.
- disease progression during or in the three months following the last administration of standard treatment, which includes fluoropyrimidine, oxaliplatin, irinotecan, bevacizumab and cetuximab or panitumumab (only if the patients had the non-mutated KRAS gene)
  - For patients who received an adjuvant treatment containing oxaliplatin, progression needed to have been reported in the six months following the end of treatment. In cases of progression occurring more than six months after the end of adjuvant treatment, patients should have received a new oxaliplatin-based treatment to be able to be included.
  - Patients for whom standard treatments needed to be discontinued due to toxicity, affecting re-administration with the same agent before disease progression, were also eligible for the study;
  - Patients with an unknown KRAS status at inclusion should have received an anti-EGFR treatment.
- metastatic colorectal cancer, measurable or immeasurable according to RECIST version 1.1 criteria
- "performance status" score ≤ 1 according to the *Eastern Cooperative Oncology Group* (ECOG) scale

- life expectancy of at lease three months
- medullary, hepatic and renal functions hardly affected (in the seven days prior to the start of treatment)
  - Total bilirubin ≤ 1.5 times the upper limit of normal (ULN);
  - Alanine transaminase (ALT) and aspartate transaminase (AST) ≤ 2.5 x ULN (or ≤ 5 x ULN for patients with liver metastases);
  - Amylase and lipase ≤ 1.5 x ULN;
  - Creatinine ≤ 1.5 x ULN;
  - Glomerular filtration rate ≥ 30 ml/min/1.73 m^2;
  - INR / activated partial thromboplastin time ≤ 1.5 x ULN;
  - Platelet count ≥ 100 000/mm^3, haemoglobin ≥ 9 g/dl, neutrophils ≥ 1500/mm^3. The transfusion of patients to achieve these inclusion criteria was not permitted.
  - Alkaline phosphatase ≤ 2.5 x ULN[1] (≤5 x ULN for patients with liver metastases).

The main non-inclusion criteria were as follows:

- previous treatment with regorafenib;
- history of cancer or concomitant cancer, distinct from the primary site or histology of CRC in the five years prior to randomisation, with the exception of curative treatment for in situ cervical cancer, skin cancer (other than melanoma) and superficial bladder tumours;
- radiotherapy expected in the four weeks, or radiotherapy limited to one field in the two weeks prior to randomisation;
- major surgery, open biopsy or significant traumatic lesions in the 28 days prior to the start of the study treatment;
- heart condition (NYHA ≥ 2 congestive heart failure, unstable angina, rhythm disorders and unmanaged hypertension);
- thrombotic disease in the six months prior to the start of the study treatment (venous thrombosis, arterial thrombosis, pulmonary embolism and stroke).

Results

Of the 760 patients randomised (505 in the regorafenib group and 255 in the placebo group), the median age was 61 years, 61% were male and all patients presented at the start of the study with an ECOG performance status (PS) of 0 or 1.
The primary localisation of the disease was the colon (65%), the rectum (29%) or both (6%). KRAS mutation was reported for 57% of patients on inclusion in the study.
More than half of patients (52%) had already been treated with two or three lines of treatment for their metastatic disease and approximately one quarter by more than five lines of treatment. Treatments included fluoropyrimidine-based chemotherapy, treatment with anti-VEGF agents and, in cases of the wild-type KRAS gene, anti-EGFR therapies.

[1] ULN: upper limit of normal.

Table 1: Disease characteristics (ITT population)

Characteristic	Placebo n = 255	Regorafenib n = 505
ECOG performance score before treatment, n (%)		
0	146 (57.3)	265 (52.5)
1	109 (42.7)	240 (47.5)
Histology, n (%)		
In situ adenocarcinoma	3 (1.2)	2 (0.4)
Adenocarcinoma	245 (96.1)	493 (97.6)
Mucous membrane carcinoma (colloid type) (more than 50% of mucous membrane carcinoma)	4 (1.6)	5 (1.0)
Adenosquamous carcinoma	1 (0.4)	1 (0.2)
Undifferentiated carcinoma	1 (0.4)	0
Unspecified carcinoma,	1 (0.4)	4 (0.8)
Primary site of the disease, n (%)		
Colon	172 (67.5)	323 (64.0)
Rectum	69 (27.1)	151 (29.9)
Colon and rectum	14 (5.5)	30 (5.9)
Missing Data	0	1 (0.2)
Stage on entry into the study, n (%)		
Stage IV	255 (100.0)	505 (100.0)
Previous anti-VEGF treatment[a] depending on CRF n (%)		
No	0	0
Yes	255 (100.0)	505 (100.0)
Time between initial diagnosis of metastatic disease and inclusion (weeks)		
Mean (range)	150.3 (10.4 to 553)	151.7 (18.1 to 837)
Median	128.5	133.1
Time between initial diagnosis of metastatic disease and inclusion (category)[a] n (%)		
< 18 months	49 (19.2)	91 (18.0)
≥ 18 months	206 (80.8)	414 (82.0)
Time between most recent progression/relapse and randomisation (weeks)		
Mean (range)	6.16 (0.3 to 52.1)	6.46 (0.1 to 50.0)
Median	4.56	4.99
Missing	9 (3.5)	30 (5.9)
KRAS Mutation, n (%)		
No	94 (36.9)	205 (40.6)
Yes	157 (61.6)	273 (54.1)
Unknown	4 (1.6)	27 (5.3)
BRAF Mutation, n (%)		
No	25 (9.8)	41 (8.1)
Yes	2 (0.8)	4 (0.8)
Unknown	228 (89.4)	460 (91.1)

Demonstration of efficacy was shown during a second predefined interim analysis (state of database on 21 July 2011), which was conducted when the study was interrupted due to positive results for the primary efficacy endpoint being achieved.

Results for the primary efficacy endpoint

The median overall survival was 6.4 months (196 days, 95% CI [178 - 222 days]) in the regorafenib group versus 5 months (151 days, 95% CI [134; 177]) in the placebo group, which is an absolute increase of 1.4 months (HR = 0.774; 95% CI [0.636; 0.942], p = 0.005178).

Secondary endpoint results

- progression-free survival

The median progression-free survival was 1.9 months in the regorafenib group versus 1.7 months in the placebo group, which is an absolute increase of 6 days in favour of regorafenib (HR = 0.494; 95% CI [0.419; 0.582], p < 0.000001).

- Objective response rate and overall management of the disease

Stabilisation of the disease was observed for 216 patients (42.8%) in the regorafenib group and for 37 patients (14.5%) in the placebo group. Five patients (1.0%) treated with regorafenib and one patient (0.4%) treated with placebo had a partial response. No complete responses were observed. There was no difference observed between the groups with regard to the objective response rate (complete response and partial response). This rate was 1.0%, 95% CI [0.3%; 2.3%] in the regorafenib group and 0.4%, 95% CI [0.0%; 2.2%] in the placebo group (95% CI [-1.74%; 0.53%], p = 0.188432).

A difference in favour of the regorafenib group was reported regarding the overall management of the disease rate (complete or partial responses or stable disease) associated with a difference in the stabilisation rate between the two groups: 41.0% (95% CI [36.7%; 45.4%]) in the regorafenib group and 14.9% (95% CI [10.8%; 19.9%] in the placebo group (95% CI [-32.06%; -19.82%] unilateral p < 0.000001).

Results for the tertiary endpoints

- Quality of life of patients

The quality of life of patients is measured with the EORTC QLQ-C30 scale. A change of ≥ 10 points on the scale was considered as being clinically significant.
On inclusion, the mean EORTC-QLQ-C30 score was 62.64 in the regorafenib group and 64.65 in the placebo group.
At the end of treatment visit, the mean EORTC-QLQ-C30 score was 48.94 in the regorafenib group and 51.85 in the placebo group.

An exploratory analysis of the sub-groups predefined in the protocol was carried out for overall survival and progression-free survival. Overall, this analysis suggests that the results are consistent in the sub-groups, in favour of regorafenib.
Analysis of the biomarkers did not enable identification of the genetic mutation or the plasma proteins capable of being a predictive factor for the activity of regorafenib.
Analysis of the main patient characteristics did not enable identification of factors predictive of the response to treatment.

08.2 Safety/Adverse effects

The rate of treatment discontinuation due to adverse events was 17.6% in the regorafenib group and 12.6% in the placebo group.
The overall incidence of serious adverse events considered as being treatment-related was higher in the regorafenib group (11.8% and 3.6% in the placebo group).
The most commonly observed adverse events (≥ 10% difference) with regorafenib compared with placebo were fatigue (63% vs. 46%), hand-foot skin reaction (47.0% vs. 7.5%), anorexia (47% vs. 28%), diarrhoea (43% vs. 17%), weight loss (32% vs. 11%), dysphonia (32% vs. 6%), hypertension (30% vs. 8%), skin rash or exfoliative rash (29% vs. 5%), mucositis or stomatitis (29% vs. 5%), fever (28% vs. 15%), hyperbilirubinaemia (20% vs. 9%), haemorrhage (20% vs.

7%) and infections (25% vs. 14%). The distribution was primarily attributed to a higher incidence of grade 1 to 3 events.
Hand-foot skin reaction was observed in 47% of patients treated with regorafenib; grade 3 was observed in 17% of patients and no grade 4 cases were reported. Hand-foot skin reaction led to permanent discontinuation of the treatment in 1.4% of cases.

08.3 Summary & discussion

Evaluation of the therapeutic benefit of regorafenib (STIVARGA) is based on a pivotal, randomised (2:1), double-blind study (CORRECT study), which compared regorafenib with placebo, both combined with the best supportive care in patients with metastatic colorectal cancer who have had disease progression after receiving all lines of standard recommended treatments.
Of the 760 patients randomised (505 in the regorafenib group and 255 in the placebo group), the median age was 61 years and all patients initially presented with an ECOG performance status (PS) of 0 or 1. There are no data for patients with a different ECOG status.
More than half of patients (52%) had already been treated with two or three lines of treatment for their metastatic disease, and approximately one quarter by more than five lines of treatment. Treatments included fluoropyrimidine-based chemotherapy, treatment with anti-VEGF agents and, in cases of the wild type KRAS gene, anti-EGFR therapies.

The primary efficacy endpoint was overall survival, defined as the time between randomisation and the death of the patient from any cause.

Demonstration of efficacy was shown during a second predefined interim analysis, which was conducted when the study was interrupted due to positive results for the primary efficacy endpoint being achieved.

In the regorafenib group, compared with the placebo group:
- the median overall survival (primary efficacy endpoint) was 6.4 months (196 days, 95% CI [178 - 222 days]) versus 5 months (151 days, 95% CI [134; 177]), which is an increase of 1.4 months (HR = 0.774; 95% CI [0.636; 0.942], p = 0.005178).
- the median progression-free survival was 1.9 months versus 1.7 months, which is an increase of 6 days in favour of regorafenib (HR = 0.494; 95% CI [0.419; 0.582], p < 0.000001).
- stabilisation of the disease was observed for 42.8% versus 14.5%.
- a partial response was observed for five patients (1.0%) versus one patient (0.4%).
- there was no difference in the objective response rate (complete and partial response) (1.0% versus 0.4%; p = 0.188432). No complete response was observed.

Evaluation of the quality of life suggested that there is no difference between the two groups.
Analysis of the main patient characteristics did not enable identification of factors predictive of the response to treatment.

The overall incidence of serious adverse events considered as being treatment-related was higher in the regorafenib group (11.8% and 3.6% in the placebo group).
The main adverse events most commonly observed (≥ 10% difference) with regorafenib compared with the placebo were fatigue (63% vs. 46%), hand-foot skin reaction (47.0% vs. 7.5%), diarrhoea (43% vs. 17%), weight loss (32% vs. 11%), dysphonia (32% vs. 6%) , hypertension (30% vs. 8%), skin rash or exfoliative rash (29% vs. 5%), mucositis or stomatitis (29% vs. 5%), fever (28% vs. 15%), hyperbilirubinaemia (20% vs. 9%), haemorrhage (20% vs. 7%) and infections (25% vs. 14%).

08.4 Planned studies

8.4.1 Risk management plan (RMP)

The RMP will focus on monitoring the following points:
- Significant identified risks: serious liver disorders; ischemic cardiac events; hypertension; haemorrhage; hand-foot skin reaction; reversible posterior leukoencephalopathy syndrome; fistula and gastrointestinal perforation; Stevens-Johnson syndrome; Lyell syndrome.
- Significant potential risks: delay in healing; interstitial lung disease; auricular fibrillation; toxicity for reproduction and development; renal impairment and photo-toxicity.
- Missing information: safety in cases of serious hepatic impairment or serious renal impairment; safety in children and patients with a history of heart problems; interaction with antibiotics and breast cancer-resistant protein substrates (BCRP).

It should be noted that in addition to routine pharmacovigilance monitoring and the presentation of continuous monitoring conclusions in the PSURs (periodic safety update reports), a phase IIIb study (study 15967) will enable additional characterisation of the incidence, the severity and the management of these events to be made.
No specific risk minimisation measures have be specified, apart from those included in the summary of product characteristics for STIVARGA.

Finally, post-authorisation monitoring measures have been approved by the European Commission. They are presented in the table below.

Table 2: Monitoring measures requested by CHMP (Committee for Medicinal Products for Human Use)

Description of monitoring measures	**Time frame**
Presentation of results of pre-specified exploratory analyses of sub-groups of wild type KRAS and mutated KRAS patients in study 15808.*	31/08/2014
Presentation of analyses of NRAS and BRAF biomarkers from study 15808, depending on the availability of samples and after obtaining informal consent from patients.	31/08/2015
In the two months following the receipt Marketing Authorisation, submission of a method that will enable assessment of additional biomarkers (study 15808).	31/10/2013
Presentation of the results of analyses of pre-specified genetic biomarkers (including NRAS, KRAS, BRAF and PIK3CA) and non-genetic biomarkers (ANG-2, IL-6, IL-8, P1GF, VEGFR-1, TIE1, VEGF-A, VEGF-C, VEGF-D, VEGF-A-121, BMP-7, VWF, M-CSF and SDF-1) from study 15983.** Analysis of genetic and non-genetic biomarkers should be mandatorily implemented for all patients included.	31/12/2020
Presentation of a protocol for the evaluation of biomarkers (study 15983).	31/10/2013

* CONCUR Study – Phase III, randomised, double-blind placebo controlled study of regorafenib and supportive care versus placebo and supportive care for Asian metastatic colorectal cancer patients who have progressed after standard treatment.
** Phase III, randomised, double-blind placebo-controlled study of the adjuvant administration of regorafenib in patients with metastatic colorectal cancer after curative removal of liver metastases.

09 THERAPEUTIC USE[2]

The National Thesaurus of Digestive Oncology[3] (TNCD), in the version dated November 2011, presents the different therapeutic strategies for patients with unresectable mCRC in progression, based on the type of chemotherapy previously administered. The strategies are presented in Table 3. Thus, after progression on chemotherapy with FOLFOX, FOLFIRI, bevacizumab, panitumumab or cetuximab, there are no further recommended alternative treatments. The TNCD recommends starting palliative care or including the patient in a treatment study.
In the version updated in February 2014, the TNCD indicates that in cases of progression with fluoropyrimidines, irinotecan, oxaliplatin and cetuximab or panitumumab and/or bevacizumab, two options are possible:

- regorafenib as monotherapy (orally administered 160 mg/day 3 weeks/4) (grade B recommendation).
- palliative care or treatment study (expert agreement).

Table 3: Therapeutic strategy proposed in the National Thesaurus of Digestive Oncology

If progression with		Therapeutic strategy proposed	Comments
LV5FU2, capecitabine, UFT or raltitrexed	→	FOLFIRI FOLFOX4 or FOLFOX6 Bevacizumab or cetuximab	Bevacizumab: in the absence of any contraindications Cetuximab: if non-mutated KRAS tumour
Bevacizumab+LV5FU2	→	FOLFIRI FOLOX4 or FOLFOX6 cetuximab	Cetuximab: if non-mutated KRAS tumour
Bevacizumab+FOLFIRI	→		
Bevacizumab+FOLFOX	→	FOLFIRI+bevacizumab FOLFIRI+panitumumab	if non-mutated KRAS tumour
Oxaliplatin	→	FOLFIRI Bevacizumab Cetuximab FOLFIRI+panitumumab	Bevacizumab: in the absence of any contraindications Cetuximab or panitumumab: if non-mutated KRAS tumour
Irinotecan	→	Cetuximab+irinotecan FOLFOX4 or FOLFOX6 XELOX Bevacizumab+FOLFOX4	Bevacizumab: in the absence of any contraindications and not administered as first line treatment
Irinotecan+cetuximab	→	Bevacizumab+FOLFOX4	Bevacizumab: in the absence of any contraindications and not administered as first line treatment
Irinotecan+oxaliplatin +/- bevacizumab	→	Cetuximab+irinotecan Panitumumab Cetuximab	Cetuximab or panitumumab: if non-mutated KRAS tumour
Fluoropyrimidines, irinotecan, oxaliplatin, cetuximab or panitumumab	→	Palliative care or treatment study	-

ESMO (*European Society for Medical Oncology*)[4] guidelines published in October 2012 specify that cetuximab may be combined with FOLFIRI or FOLFOX when panitumumab cannot be combined with FOLFOX. These treatments can only be administered to patients with the non-mutated KRAS gene.

<u>The therapeutic use of STIVARGA</u>:

According to its Marketing Authorisation, STIVARGA is a treatment for patients who have been previously treated with, or are not considered candidates for available therapies in particular fluoropyrimidine-based chemotherapy, an anti-VEGF therapy and an anti-EGFR therapy.

[2] http://www.e-cancer.fr/publications/55-recommandations-de-pratique-clinique/730-rapport-integral-melanome-cutane-metastatique.
[3] National Thesaurus of Digestive Oncology (14/10/2011) Available at http://www.snfge.com/data/ModuleDocument/publication/5/pdf/TNCD-chapitre-4.pdf. Consulted on 11 July 2012.
[4] Schmoll HJ, van Cutsem E, Stein A et al. ESMO Consensus Guidelines for management of patients with colon and rectal cancer. A personalized approach to clinical decision making. Annals of Oncology 2012; 23: 2479–2516.

Given the modest activity at the cost of significant toxicity, it may only be proposed for patients previously treated with all available therapies. In addition, as there are no data for patients with an ECOG score > 1, it should only be proposed for patients with a performance score of 0-1.

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

◗ Metastatic colorectal cancer is a serious and life-threatening disease.

◗ This medicinal product is intended as curative therapy specifically for metastatic colorectal cancer.

◗ The efficacy/adverse effects ratio is modest.

◗ There are no validated medicinal treatment alternatives for this stage of the disease.

◗ This is a rescue treatment.

◗ Public health benefit:
Colorectal cancer (CRC) is a serious and common clinical presentation that is a major burden on public health. The burden of metastatic colorectal cancer is substantial. The burden on the population of patients likely to benefit from this proprietary medicinal product (patients with metastatic CRC previously treated with or not considered as candidates for available treatments in particular fluoropyrimidine-based chemotherapy, an anti-VEGF therapy and an anti-EGFR therapy) may also be considered as substantial.
Improvement in the management of this disease is a public health need which is an established priority (French Public Health Law of 2004, Cancer Plan, Plan for improving the quality of lives of patients with chronic conditions).
In view of the available data from the double-blind, placebo-controlled superiority study on pre-treated patients showing, in particular, a modest improvement in overall survival and progression-free survival (1.4 months and 6 days respectively), stabilisation of the disease most commonly at the cost of considerable toxicity, it is not expected that this and a proprietary medicinal product will provide any additional impact in terms of morbidity and mortality or quality of life.
The transferability of results from studies to clinical practice is acceptable.
No impact on the organisation of healthcare is expected.
It is therefore difficult to determine whether STIRVARGA will be able to provide an additional response to the identified public health need.
Consequently, in the current state of knowledge, it is not expected that STIVARGA will benefit public health in this indication.

Taking account of these points, the Committee considers that in the treatment of metastatic colorectal cancer after failure with or in patients not considered candidates for available therapies, in particular fluoropyrimidine-based chemotherapy, an anti-VEGF therapy and an anti-EGFR therapy, the actual benefit of STIVARGA is:

- **low for patients whose performance score is 0-1**
- **insufficient for patients whose performance score is > 1**.

010.2 Improvement in actual benefit (IAB)

Given the safety profile and the low level of effect, the Committee considers that STIVARGA does not provide any improvement in actual benefit (level V, non-existent) in the treatment of metastatic colorectal cancer patients with failed treatments with or not considered candidates for available therapies (fluoropyrimidine-based chemotherapy, an anti-VEGF therapy and an anti-EGFR therapy) and whose performance score is 0 or 1.

010.3 Target population

The target population of STIVARGA is represented by metastatic colorectal cancer (mCRC) patients with failed treatments with or not considered candidates for available therapies (fluoropyrimidine-based chemotherapy, an anti-VEGF therapy and an anti-EGFR therapy) and whose performance score is 0 or 1.
A study carried out on the period between 2011 and 2012 by Kantar Health, based on a sample size of 1421 patients and then extrapolated to the total population of patients presenting with mCRC, enables the annual number of patients who have been treated for their mCRC with all of the validated treatments to be estimated as 8100 patients.
An alternative approach to calculate the target population can be based on the target population used by the Transparency Committee in their previously issued Opinions (VECTIBIX, dated 30 April 2008) in which it is stated that third line chemotherapy is started for approximately half of metastatic CRC patients, which represents approximately 10,500 patients.
It is estimated that one quarter of patients (opinion of experts) at this stage of the disease have a performance score > 1 and therefore are not considered candidates for treatment with STIVARGA.
Consequently, the target population for STIVARGA is estimated as being between 6400 and 7800 patients per year.

011 TRANSPARENCY COMMITTEE RECOMMENDATIONS

The Committee recommends inclusion of STIVARGA tablets on the list of medicines refundable by National Health Insurance and approved for hospital use in the treatment of metastatic colorectal cancer patients with failed treatments with or not considered candidates for available therapies (fluoropyrimidine-based chemotherapy, an anti-VEGF therapy and an anti-EGFR therapy) and whose performance score is 0 or 1.

◗ Packaging

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

◗ Proposed reimbursement rate: 100%