HAUTE AUTORITÉ DE SANTÉ

**The legally binding text is the original French version**

**TRANSPARENCY COMMITTEE**

OPINION

3 October 2012

***The draft opinion approved by the Transparency Committee on 6 June 2012 was examined at a hearing on 3 October 2012***

**TEYSUNO 15 mg/4.35 mg/11.8 mg, hard capsules**
**B/42 (CIP code: 219 461 7)**

**TEYSUNO 15 mg/4.35 mg/11.8 mg, hard capsules**
**B/126 (CIP code: 219 462 3)**

**TEYSUNO 20 mg/5.8 mg/15.8 mg, hard capsules**
**B/42 (CIP code: 219 464 6)**

**TEYSUNO 20 mg/5.8 mg/15.8 mg, hard capsules**
**B/84 (CIP code: 219 465 2)**

**Applicant: NORDIC PHARMA SAS**

tegafur, gimeracil and oteracil
ATC code: L01BC53 (pyrimidine analogue)

List I
Medicine for hospital prescription only. Prescription restricted to oncology or haematology specialists or doctors with cancer training. Medicine requiring special monitoring during treatment.

Date of Marketing Authorisation (centralised procedure): 14 March 2011

Reason for request: Inclusion on the list of medicines refundable by National Health Insurance and approved for hospital use.

Medical, Economic and Public Health Assessment Division

## 1. CHARACTERISTICS OF THE MEDICINAL PRODUCT

### 1.1. Active ingredient

Each capsule contains tegafur, gimeracil and oteracil

### 1.2. Indication

"TEYSUNO is indicated in adults for the treatment of advanced gastric cancer when given in combination with cisplatin."

### 1.3. Dosage

"The recommended standard dose for TEYSUNO when administered in combination with cisplatin is 25 mg/$m^2$ (expressed as tegafur content) twice daily, morning and evening, for 21 consecutive days followed by 7 days rest (= 1 treatment cycle). This treatment cycle is repeated every 4 weeks.

The recommended dose of cisplatin with this regimen is 75 mg/$m^2$ by intravenous infusion administered once every 4 weeks. Cisplatin should be discontinued after 6 cycles, without withdrawal of TEYSUNO. If cisplatin is discontinued before 6 cycles, TEYSUNO treatment alone can be resumed when the criteria for restarting it are met."

## 2. SIMILAR MEDICINAL PRODUCTS

### 2.1. ATC Classification (2011)

| | |
|---|---|
| L | Antineoplastic and immunomodulating agents |
| L01 | Antineoplastic agents |
| L01B | Antimetabolites |
| L01BC | Pyrimidine analogues |
| L01BC53 | Tegafur, combinations |

### 2.2. Medicines in the same therapeutic category

Comparator medicines (pyrimidine analogues):

- XELODA (capecitabine) Substantial AB – IAB V "Given the absence of data demonstrating the superiority of Xeloda versus 5 Fluorouracil, the Committee considers that Xeloda does not provide an improvement in actual benefit compared with the comparator product", TC Opinion of 16 February 2008.
- FLUOROURACIL ICN (5 fluorouracil) and its generics

### 2.3. Medicines with a similar therapeutic aim

Cytotoxics used primarily within the context of combinations:

1/ Anthracyclines:
- FARMORUBICIN (epiribucin) and its generics

2/ Platinum salts:
- Cisplatin:
- Oxaliplatin (ELOXATIN) (Temporary Treatment Protocol in the national good practice guidelines in gastric cancer research up to March 2010, date of removal of oxaliplatin from the list of medicinal products in addition to DRG).

3/ Taxanes:
- TAXOTERE (docetaxel)

## 3. ANALYSIS OF AVAILABLE DATA

The submitted dossier comprises:

- a pharmacokinetic study S1101 which, due to its aims, will not be presented in this opinion,
- a pivotal study, the results from which are analysed below.
- the dossier also cites the results from efficacy and safety trials, carried out with other medicinal products (capecitabine or fluorouracil). However, in the absence of a formalised comparison, these data cannot be taken into consideration.

### 3.1. Efficacy

**S1 301 FLAGS Study**

An open-label, randomised study that compared TEYSUNO with fluorouracil (5-FU), both of which were administered in combination with cisplatin to patients with advanced gastric cancer, not previously treated by chemotherapy.

The primary efficacy endpoint was overall survival, defined as the time between randomisation and death.

The secondary endpoints were:

- objective response rate (complete or partial, confirmed according to RECIST criteria[1]),
- progression-free survival, defined as the time between randomisation and the date of the occurrence of the first documented progression of the disease or death, in the absence of documented progression.
- time to treatment failure, defined as the time between randomisation and the date of permanent discontinuation of the study treatment or the comparator medicine, the first documented occurrence of disease progression (based on imaging alone and evaluated by an independent review), or death, whichever comes first.
- safety.

The two study treatments were:

Group 1: - TEYSUNO 25 mg/m², twice daily, given orally on Days 1 to 21, followed by a recovery period of 7 days from Day 22 to Day 28, combined with cisplatin 75 mg/m² administered via IV infusion over one to three hours on Day 1 after TEYSUNO has been taken.

Group 2: - 5-FU: 1000 mg/m²/24 hours administered via continuous IV infusion over 120 hours from Day 1 to Day 5, combined with cisplatin 100 mg/m² administered via IV infusion over one to three hours on Day 1.

These treatments were repeated every 4 weeks for a maximum of 6 cycles.

Treatment was continued until the occurrence of disease progression or toxicity deemed to be unacceptable by the clinical investigator.

The main inclusion and non-inclusion criteria were as follows:

[1] RECIST : Response Evaluation Criteria In Solid Tumours:

- Full response: disappearance of all tumour lesions
- Partial response: reduction of 30% in the largest lesion diameter
- Disease progression: increase of 20% in largest lesion diameter
- Stable disease: changes in tumour size not meeting the conditions indicated previously.

The following patients could be included:

- patients aged ≥ 18 years, with unresectable, locally advanced (Stage IV) or metastatic gastric or gastroesophageal cancer, confirmed histologically,
- patients with an ECOG status 0 or 1 who were able to meet the minimal requirements necessary to perform laboratory tests,
- patients who had not received previous chemotherapy treatment for advanced gastric cancer with cytotoxic products,
- patients who had not had radiotherapy within the past 4 weeks or major surgery within the past 3 weeks.

The following patients could not be included:

- patients who had received treatment for cancer during the last 5 years (chemotherapy, bone marrow irradiation > 25%).
- patients with other serious medical conditions (another tumour occurring less than 5 years previously, nausea, vomiting, diarrhoea, psychiatric disorder, etc.).
- patients who had taken concomitant treatment that may interact with TEYSUNO, 5-FU or cisplatin.
- patients with a known hypersensitivity to 5-FU or cisplatin.

**Results:**

The 1029 patients included had a median age of 59 years and 14.2% of patients were aged over 70 years. Nearly three quarters of patients (70.8%) were male.
The tumour was gastric in 83% of cases and was located in the gastroesophageal junction in 16.5% of cases.

Table 1: Overall survival and progression-free survival in the FLAGS Study (superiority test)

| | TEYSUNO/cisplatin N=521 | 5 FU/cisplatin N=508 | HR (95% CI) |
|---|---|---|---|
| Evaluation Criteria | | | |
| Median overall survival (months) | 8.6 [7.9; 9.5] | 7.9 7.9 [7.2; 8.5] | 0.92 [0.80; 1.05] |
| Progression-free survival (months) | 4.8 [4.0; 5.5] | 5.5 [4.4; 5.8] | 0.99 [0.86; 1.14] |

There was very little difference in median overall survival (primary endpoint) between the two groups: 8.6 months in the TEYSUNO group versus 7.9 months in the 5 FU group (HR = 0.92, 95% CI: [0.80; 1.05]). As this was a superiority study, the primary objective was not achieved.

As the primary objective of the study was not achieved, the results for the secondary endpoints, which include safety, are provided for information only:

- the response rate was similar between the two groups (117/402 patients evaluated (29.1%) in the TEYSUNO group and 123/385 patients evaluated (31.9%) in the 5 FU group).
- the median progression-free survival was similar between the two groups (4.8 months in the TEYSUNO group versus 5.5 months in the 5 FU group; HR = 0.99; 95% CI [0.86 - 1.14]).
- the median time to treatment failure was 3.8 months (95% CI [3.7 - 4.0]) for patients in the TEYSUNO group versus 3.8 months (95% CI [3.7 - 4.4]) in the 5 FU group (HR: 0.87, 95% CI [0.77 – 0.99]).
- the overall FACT-Ga score, which evaluates quality of life was also similar between the two groups.

Due to these results, the applicant has carried out an analysis, which was not planned for in the protocol, on the non-inferiority of TEYSUNO versus 5 FU.

This statistical analysis is based on the following hypothesis: non-inferiority is established if the upper 95% confidence interval limit for the relative risk is below 1.10.
The hazard ratio (HR) was 0.92 ([0.80 – 1.05]) with an upper 95% confidence interval limit of 1.05 which is below the 1.10 limit proposed and thus suggests the non-inferiority of TEYSUNO compared with 5 FU.

### 3.2. Adverse effects

The overall incidence of adverse events (all grades, and regardless of the cause) was comparable between the two groups (TEYSUNO/cisplatin, 98.7%; 5 FU/cisplatin, 99.2%).
Treatment was stopped due to an adverse event by 56 patients in the TEYSUNO group (10.7%) and by 73 patients in the 5 FU group (14.4%).
The most commonly reported adverse events in the TEYSUNO group were: nausea (61.6%), vomiting (48.0%), anaemia (44.0%), fatigue (39.3%), and anorexia (31.5%), and in the 5 FU group the adverse effects were: nausea (67.3%), vomiting (55.3%), neutropenia (47.2%), anaemia (46.1%), and fatigue (39.4%).
The incidence of grade 3-4 stomatitis/mucositis was 2.1% in the TEYSUNO group and 21.5% in the 5 FU group. The incidence of grade 3-4 diarrhoea was 4.8% in the TEYSUNO group and 4.5%, in the 5 FU group. The incidence of grade 3-4 hyperbilirubinaemia was 6.5% in the TEYSUNO group and 3.6% in the 5 FU group. Grade 3-4 hypercreatinaemia was noted in 0.8% of patients in the TEYSUNO group versus 2.2% of patients in the 5 FU group.
It should be noted that the dose of cisplatin used in the TEYSUNO group (75 mg/m²) was lower (25% less) than in the comparator medicine group (100 mg/m$^2$). An impact on the comparison of the safety profiles, especially concerning haematology, cannot be ruled out.

### 3.3. Conclusion

An open-label randomised study carried out on patients with previously untreated advanced gastric cancer compared chemotherapy combining TEYSUNO / cisplatin at a dose of 75 mg/m² to that combining fluorouracil (5-FU) / cisplatin at a dose of 100 mg/m².

The regimen for this study did not allow the effects of TEYSUNO versus 5 FU to be identified due to the fact that the dose of cisplatin was different between the two groups (25% less in the TEYSUNO group).

The 1029 patients included had a median age of 59 years, 14.2% of patients were aged over 70 years and 70.8% were male.
The tumour was gastric (83%) or in the gastroesophageal junction (16.5%).

The median overall survival (primary endpoint) was similar across the two groups: 8.6 months in the TEYSUNO group versus 7.9 months in the 5 FU group (HR = 0.92 [95% CI: 0.80; 1.05]). The primary superiority objective was not achieved in a prospective analysis; the results for the secondary endpoints, including safety, were of an exploratory nature and did not allow any conclusions to be drawn.

The applicant investigated the non-inferiority of TEYSUNO versus 5 FU in an analysis that was not planned for in the protocol. The hazard ratio (HR) was 0.92 (95% CI [0.80 – 1.05]), i.e. an upper limit of the 95% confidence interval which is below the limit of 1.10 defined for the non-inferiority of TEYSUNO compared with 5 FU. The Committee has highlighted that the investigation into non-inferiority based on a superiority analysis can only be accepted if it was already recorded in the protocol.

Safety data is therefore for information only:
- the overall incidence of adverse events of any grade were comparable between the two groups (TEYSUNO/cisplatin 75 mg/m², 98.7%; 5 FU/cisplatin 100 mg/m², 99.2%).
- treatment was stopped due to an adverse event by 56 patients in the TEYSUNO/cisplatin 75 mg/m² group (10.7%) and by 73 patients in the 5 FU/cisplatin 100 mg/m² (14.4%) group.

## 4. TRANSPARENCY COMMITTEE CONCLUSIONS

### 4.1. Actual benefit

Gastric cancer is a serious and life-threatening disease.
These proprietary medicinal products are intended as curative therapy.
It is a first-line treatment.

Public health benefit:

The public health burden of metastatic gastric adenocarcinoma is substantial.
Improved treatment is a public health need which is included in the Cancer Plan and the national development programme for palliative care.
Available data do not show the impact of TEYSUNO in terms of a reduction in morbidity and mortality or the improvement in quality of life; therefore it is not expected that this medicinal product will have an additional impact compared with current treatments.
Consequently, is not expected that TEYSUNO will benefit public health in this indication.

The efficacy/adverse effects ratio for these medicinal products is low.
Alternative medicinal products exist.

In view of:

- the limited data available from a study not allowing the performance of TEYSUNO to be evaluated: study design not highlighting the effects of TEYSUNO itself versus 5 FU, due to the fact that the dose of cisplatin was different between the two groups (25% less in the TEYSUNO group).
- the absence of data on its use with other medicinal products, especially trastuzumab, farmorubicin (E) and docetaxel (D) leading to difficulties in introducing this medicinal product into the current therapeutic strategy in the treatment of gastric adenocarcinomas.[2] This is currently based on an evaluation of HER2 status before a treatment decision is made and specifies, in cases of HER2 positive marking, a combination of trastuzumab, 5 fluoruracil (F) and cisplatin (C), or in cases of negative marking, an ECF, DCF-type combination.

Taking into account all of this information and after a discussion and voting, the Committee considers that the actual benefit is insufficient to justify reimbursement by National Health Insurance.

### 4.2. Improvement in actual benefit (IAB)

Not applicable

### 4.3. Transparency Committee recommendations

The Transparency Committee does not recommend inclusion on the list of medicines refundable by National Health Insurance and on the list of medicines approved for hospital use and various public services.

[2] http://www.snfge.org/data/ModuleDocument/publication/5/pdf/TNCD-chapitre-2.pdf