HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

17 January 2007

UBIT 100 mg, film-coated tablet
Box of 1 - CIP: 372 223-1
Box of 10 - CIP: 567 675-9
Box of 20 - CIP: 567 676-5
Box of 100 - CIP: 567 677-1

Applicant : OTSUKA PHARMACEUTICAL EUROPE Ltd

^{13}C-urea

List I

Date of Marketing Authorisation: March 8, 2006

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

Health Technology Assessment Division

1 CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient

^{13}C-urea

1.2. Indication

UBIT is used for the *in vivo* diagnosis of gastroduodenal *Helicobacter pylori* infection.

1.3. Dosage

UBIT 100 mg is a film-coated tablet for oral administration.

The *in vivo* diagnosis is a ^{13}C-urea breath test. The dosage for adults is 1 film-coated tablet taken with 100ml of plain water, without biting or chewing the tablet. The patient should be fasting (no food or beverage) prior to taking the tablet for at least 8 hours, to be taken preferably first thing in the morning.

The film-coated tablet should be swallowed whole and not chewed.

It is essential to follow correctly the instruction for use in order to ensure reliability of the test results. In case it is necessary to repeat the test procedure, this should not be performed earlier than the following day.

1.4. Pharmacodynamic properties

The bacterial urease produced in the stomach by *Helicobacter pylori* hydrolyses urea into ammonia and bicarbonate. Gastric acidity transforms most of the bicarbonate into carbon dioxide that is absorbed, transported to the lungs, and then exhaled.
Ingestion of marked urea in a *Helicobacter pylori* infected patient allows this isotope, which is stable in the exhaled carbon dioxide, to be measured.
The difference in the proportions of ^{13}C and ^{12}C (reflecting the isotopic enrichment of exhaled air) before and after absorption of marked urea allows the positivity threshold to be determined. Values above this level point to the presence of *Helicobacter pylori* (this threshold is set at 2.5‰).

2 SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification (2005)

This product is not listed in the ATC, but it can be regarded as similar to:

V: Various
09: Diagnostic radiopharmaceuticals
H: Inflammation and Infection Detection
X: Other diagnostic radiopharmaceuticals for inflammation or infection detection

2.2. Medicines in the same therapeutic category

^{13}C-urea breath test products with Marketing Authorisation are the following:

DCI	Medicinal Product	Pharmaceutical Formulation Route of Administration	Indication
^{13}C-urea 100 mg	Pylobactell®	Soluble tablet Oral administration	This medicine is intended for diagnostic use only. For an *in vivo* diagnosis of gastrointestinal *Helicobacter pylori* infection.
^{13}C-urea 75 mg	Helicobacter Test INFAI®	Powder for oral solution Oral administration	Helicobacter Test INFAI may be used for the in vivo diagnosis of gastroduodenal *Helicobacter pylori* infection
^{13}C-urea 75 mg	HELIKIT 75mg®	Powder for oral solution Oral administration	*In vivo* diagnosis of *Helicobacter pylori* infection, particularly monitoring of its eradication

2.3. Medicines with a similar therapeutic aim

Tests used to diagnose *Helicobacter pylori* include:

- Invasive tests: endoscopy with biopsy (culture, rapid urease test, histology)
- Non-invasive tests: serology

3 ANALYSIS OF AVAILABLE DATA

3.1. Efficacy

For its medicinal product UBIT, the laboratory has submitted 5 studies, two of which are clinical pharmacology studies, one was a comparative study of two spectrophotometry methods for measuring ^{13}C, one study was an open-label without statistical analysis, and one was an open-label phase III study (255 patients, unpublished study).

Only the phase III study (open-label, cross-over study to establish equivalence) was retained. This compared the diagnostic performance of UBIT tablets to that of UBIT granules for oral solution in patients with a scheduled endoscopy for suspected gastroduodenal disease, according to the administration modalities and measures established in the SPC.
Primary endpoints were:

- Evaluation of UBIT tablet diagnostic performance compared to the biopsy used as reference
- Evaluation of UBIT tablet diagnostic performance compared to that of UBIT granules for oral solution used as reference
- Evaluation of UBIT granules for oral solution diagnostic performance compared to the biopsy used as reference

Compared to the biopsy used as reference, the results demonstrated that for UBIT tablet sensitivity was 97.7% (95% CI [93.4-99.5]), specificity was 98.4% (95% CI [94.3-99.8]) and accuracy was 98.0% (95% CI [95.5-99.4]) in terms of diagnostic performance.

Compared to UBIT granules for oral solution used as reference, the results demonstrated that for UBIT tablet sensitivity was 96.9% (95% CI [92.1-99.1]), specificity was 97.6% (95% CI [93.0-99.5]) and accuracy was 97.2% (95% CI [94.3-98.9]).

Table 1: Results for each group:

		Patient status		***Total***	***Accuracy (%) (95% CI)***
		Infected	*Non-infected*		
UBIT tablet	*Positive*	124	2	126	98.0 (95.4-99.4)
	Negative	3	121	124	
	Total	127	123	250	
UBIT oral solution	*Positive*	124	3	127	97.6 (94.9-99.1)
	Negative	3	120	123	
	Total	127	123	250	

The difference in terms of accuracy between UBIT tablet and UBIT oral solution, using the biopsy as reference, was 0.4% (95% CI of the difference [-1.7; 2.5%] including value 0).
These results suggest the equivalence of both pharmaceutical formulations in terms of diagnostic performance.

3.2. Adverse events

According to the SPC,

Clinical trials

Causally related adverse events were reported in only 8 of the 1,150 patients included in clinical trials with the urea breath test. These included abdominal distension, diarrhoea, epigastric discomfort and increased serum potassium.

Post-Marketing Authorisation data

Nausea and vomiting have very rarely been reported (≤ 1/10 000).

Isolated incidents (≤ 1/10 000) of dyspnoea, urticaria, rash, facial oedema, and hot flushes have been reported. These symptoms could indicate an anaphylactic reaction.

3.3. Conclusion

Under the conditions for use described in the SPC, calling for rinsing of the mouth immediately following ingestion of the granules for oral solution and analysis of the breath sample 20 minutes following ingestion of the oral pharmaceutical formulation, UBIT tablet was found to be equivalent to UBIT granules for oral solution in terms of diagnostic performance.

4 TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit

Helicobacter pylori infection is associated with the development of gastric and duodenal ulcers and the onset of stomach cancers. Complications are serious and can be life-threatening.

This product is intended for diagnostic use.

The efficacy/undesirable effects ratio is high.

This medicinal product is a first-line product for those few patients that require a non-invasive diagnostic method as an initial step.
In accordance with the recommendations, it is mainly used to monitor the eradication of *Helicobacter pylori* following treatment for a duodenal infection.

Diagnostic alternatives for this medicinal product exist (invasive and non-invasive methods).

> In terms of public health, the burden imposed by *Helicobacter pylori* infections cannot be quantified. It is, in all probability, moderate. However, the number of patients unable to undergo fibroscopy as a first-line procedure and must, therefore initially have recourse to a non-invasive method, is small. Therefore, the burden represented by the patients affected by this indication is low.
> UBIT® is a test that results in a reliable diagnosis of *Helicobacter pylori* infection. The rate of morbidity prevented on account of a *Helicobacter pylori* diagnosis cannot be directly quantified but is, in all probability, moderate. The number of complications avoided on account of a urea test of this type in patients who are unable to undergo a fibroscopy examination is unknown. However, due to the fact that gastric fibroscopy remains, in France, recommended as a first-line procedure, the public health benefit expected for this medicinal product affects only this patient sub-population and thus, can only be low, as is the case with other urea tests.
> Should the French recommendations be amended, this public health interest would, accordingly, be revised.

The actual benefit is substantial.

4.2. Improvement in actual benefit

The UBIT tablet does not provide an improvement in actual benefit (IAB V) compared to UBIT granules for oral solution.

4.3. Therapeutic use

For the *in vivo* diagnosis of *Helicobacter pylori*, the available recommendations[1,2] favour invasive methods for the initial diagnosis of the infection and restrict the use of a urea breath test to monitor the eradication of *Helicobacter pylori*. This strategy is based on the fact that an endoscopy allows mucous lesions to be visualised and subjected to histological analysis.
Nevertheless, there are clinical conditions that justify recourse to a first-line non-invasive procedure, in particular:

- If performance of biopsies is contraindicated (patient on anticoagulant treatment),
- Where endoscopy has been performed but doubt persists as to whether *Helicobacter pylori* infection is present (in particular, with biopsies performed while the patient was on anti-secretory treatment),
- To ascertain whether first-degree relatives of patients with gastric cancer are *Helicobacter pylori* infected,
- In case endoscopy is refused.

In France, ^{13}C urea breath tests are recommended only to monitor the eradication of *Helicobacter pylori* when endoscopy is not necessary[1, 2]. The test must be undertaken 4 to 6 weeks following the end of the anti-secretory or antibiotic treatment.

4.4. Target population

French recommendations advocate the use of the test to monitor the eradication of *Helicobacter pylori*. Each year there are between 60,000 and 80,000 new cases of duodenal ulcers and 15,000 to 20,000 new cases of gastric ulcers. 90% of patients with duodenal ulcers and 70% of patients with gastric ulcers are probably infected with *Helicobacter pylori*[3]. In total, **64,500 to 86,000 new patients** each year would be likely to benefit from a ^{13}C urea breath test.

Data on use of the test for the initial diagnosis of *Helicobacter pylori* infection is not available. In all probability the number of patients is low. In light of the current official French recommendations, it does not seem appropriate to increase the estimate number of patients likely to benefit from ^{13}C urea breath tests.

[1] CANARD J.M. et al. Recommandations de la SFED. Places respectives de l'endoscopie et du test respiratoire dans le diagnostic et le contrôle de l'éradication d'*Helicobacter pylori*. September 2003.
[2] Conférence de consensus *Helicobacter pylori* Révision 99. Conclusions et recommandations révisées du groupe de travail. *Gastroenterol Clin Biol 1999; 23: C95-C104*
[3] AFSSAPS – RBP – Les antiulcéreux chez l'adulte - Révision 99.

4.5. Transparency Committee recommendations

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The Transparency Committee recommends inclusion on the list of medicines reimbursed by National Insurance and on the list of medicines approved for use by hospitals and various public services for the indication and at the dosage indicated in the Marketing Authorisation.

Packaging: Only the single tablet blister package is approved for external prescription conditions.

Rate of reimbursement: 65 %

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The Transparency Committee recommends inclusion on the list of medicines approved for hospital use and various public services for the indication and dosage of the Marketing Authorisation.