HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

13 December 2006

HELIKIT 75 mg, powder for oral solution
CIP : 343 132-1

Applicant : MAYOLY SPINDLER

[13] Curea anhydrous citric acid

List I

Marketing Authorisation date: 29 May 1997
Marketing Authorisation revision: 29 March 2006

Reason for request: inclusion on the list of medicines reimbursed by National Insurance and approved for use by hospitals in the extension of indication*: "In-vivo diagnosis of Helicobacter pylori infection"*

Health Technology Assessment Division

1 CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient

^{13}C urea	:	75 mg
Anhydrous citric acid	:	1.4 g

1.2. Indication

Old text:
Monitoring of *Helicobacter pylori* eradication

New text:
In-vivo **diagnosis of *Helicobacter pylori* infection, particularly monitoring of its eradication.**

Refer to the official recommendations for the treatment of *Helicobacter pylori* infections.

1.3. Dosage

For adults only.
Oral route: 1 dose of citric acid and 1 dose of ^{13}C-labelled urea.
The test must be performed at a medical analysis laboratory.
Subjects due to undergo the breath test must fast from the previous day.

The HELI-KIT test is performed *in vivo* to diagnose *Helicobacter pylori* infection; it cannot be used to draw any conclusions as to the pathology associated with *Helicobacter pylori* infection.

1.4. Pharmacodynamic properties

The bacterial urease produced in the stomach by *Helicobacter pylori* hydrolyses urea into ammonium and bicarbonate. Under the gastric acidity effect, most of the bicarbonate is transformed into carbon dioxide which is absorbed, carried to the lungs and then exhaled.

Ingestion of labelled urea by a patient with *Helicobacter pylori* infection allows this isotope, which is stable in 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 labelled urea allows the positivity threshold to be determined. Values above that threshold, indicate the presence of *Helicobacter pylori* (this threshold is normally set at 5‰). Ingestion of citric acid slows down the emptying of the stomach, thus prolonging the duration of interaction between bacterial urease and ^{13}C urea.

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 and infection detection

2.2. Medicines in the same therapeutic category

A Marketing Authorisation has been granted for the following ^{13}C-labelled urea breath tests (^{13}C UBT):

INN	Proprietary product	Pharmaceutical form Administration route	On the market	Indication
^{13}C urea 75 mg	Helicobacter Test INFAI®	Powder for oral solution Oral route	No	The Helicobacter Test INFAI can be used for in-vivo diagnosis of gastroduodenal infection involving *Helicobacter pylori*
^{13}C urea 100 mg	Pylobactell®	Soluble tablet Oral route	No	This drug is for diagnostic use only. For *in-vivo* diagnosis of gastrointestinal infection caused by *Helicobacter pylori.*
^{13}C urea 100 mg	Ubit 100mg®	Granules to be dissolved in 100 ml of water Oral route	No	In-vivo diagnosis of *Helicobacter pylori* infection

2.3. Medicines with a similar therapeutic aim

The tests used to diagnose *Helicobacter pylori* are:

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

3 ANALYSIS OF AVAILABLE DATA

No study performed with HELI-KIT® is available. The diagnostic performance of HELI-KIT® has been demonstrated on the basis of bibliographical analysis of nine published studies[1,2,3,4,5,6,7,8,9] in which the ^{13}C UBT was performed according to methods that were identical or very similar to those recommended in the HELI-KIT® SPC: 75 mg of ^{13}C urea administered to a fasting subject with citric acid, analysis of exhaled air performed 30 minutes after administration of the substrate and positivity threshold set at 5‰. The main difference between these nine studies was the positivity threshold, which ranged from 3.5 to 5‰.

3.1. Efficacy

3.1.1. Data synthesis

1,787 adult patients with dyspepsia were evaluated in the context of an initial diagnosis of *Helicobacter pylori* infection.

The ^{13}C UBT was assessed in comparison with the benchmark of the endoscopy results. In eight studies, patients were considered to be carriers of *Helicobacter pylori* infection (Hp+) if they had a positive culture or, in the event of a negative culture, if they had a specific positive histology (His+) and a positive rapid urease test (CLO+). In one study [the d'Elios study carried out in 2000], Hp+ status was based solely on histology results from four biopsies.

Results:

Table 1 shows the performance of ^{13}C UBT carried out according to identical or very similar methods to those recommended in the HELI-KIT® SPC in each of the nine analysed studies.

[1] D'ELIOS M. et al. Usefulness of 13C-Urea breath test in the diagnosis of gastric *helicobacter pylori* infection, *Int J Immunol Pharmacol 2000*; 13 (1) : 27-30

[2] SAVARINO V et al. Comparison of isotope ratio mass spectrometry and nondispersive isotope selective infrared spectroscopy for 13C-urea breath test. *Am J Gastroenterol. 1999*;94:1203-8.

[3] SAVARINO V et al. Isotope ratio mass spectrometry (IRMS) versus laser-assisted ratio analyzer (LARA): a comparative study using two doses of. of 13C urea and two test meals for pre and posttraitement diagnosis of Helicobacter pylori infection, *Dig Dis Sci. 2000*; 45: 2168-74.

[4] WONG WM et al. 13C-urea breath test without a test meal is highly accurate for the detection of Helicobacter pylori infection in Chinese. *Aliment Pharmacol Ther. 2000*;1:1353-8.

[5] LEODOLTER A. et al. Validity of a modified 13C-urea breath test for pre- and post-treatment diagnosis of helicobacter pylori infection in the routine clinical setting *Am J Gastroenterol 1999*; 94(8): 2100-2104

[6] LEODOLTER A. et al. Citric acid or orange juice for the 13C-urea breath test : the impact of pH and gastric emptying. *Aliment Pharmacol Ther 1999*; 13 : 1057-1062

[7] DOMINGUEZ-MUNOZ J.E. et al. A citric acid solution is an optimal test drink in the 13C-urea breath test for the diagnosis of Helicobacter pylori infection. *Gut 1997*; 40 : 459-462

[8] GATTA L et al Effect of proton pump inhibitors and antacid therapy on 13C urea breath tests and stool test for Helicobacter pylori infection. *Am J Gastroenterol. 2004*;99:823-9.

[9] MONTEIRO L. et al. Diagnostic of Helicobacter pylori infection : non invasive methods compared to invasive methods and evaluation of two new tests *Am J Gastroenterol 2001*; 96 (2) : 353-358

Table 1: Performance of ^{13}C UBTs carried out with 75 mg of ^{13}C urea administered to fasting subjects with citric acid and IRMS assessment after 30 minutes

Author	N	Threshold (‰)	Sensitivity (%)	Specificity (%)	PV+ (%)	PV- (%)	Accuracy (%)
D'Elios,2000	492	4	97.4	98.5	98.2	97.2	98.0
Savarino, 1999	134	5	98.6	98.3	98.6	98.3	98.5
Savarino, 2000	105	5	98	97	98	97	98
Wong, 1999	202	5	96.5	97.7	98.2	95.6	97.0
Leodolter (1999a)	553	4	94.7	97.8	96.7	96.5	96.6
Leodolter (1999b)	50	4	100	100	100	100	100
Dominguez-Munoz, 1997	80	4	100 92.6-100*	100	100	100	100
Gatta, 2004	72	4.5	100	100	–	–	–
Monteiro, 2001	99	3.5	93.3 88.4-98.2*	98.1 95.5-100*	97.7	94.6	95.5
Median values (CV%) (Range)			98 (2.47) 93.3-100	98.5 (1.15) 97-100	98.2 (1.14) 96.7-100	97 (2.15) 94.6-100	98 (1.74) 95.5-100

* 95% CI

The median values of the five performance criteria of the test were ≥ 97%.

Sensitivity ranged from 93.3% to 100%, and specificity was at least 97%. The variation coefficients did not exceed 2.5%, indicating a very good degree of reproducibility of the ^{13}C UBT between research teams.

Consequently, the ^{13}C UBT conducted by administering 75 mg of ^{13}C urea with citric acid and performing an IRMS assessment of exhaled air after 30 minutes with positivity thresholds between 3.5‰ and 5‰ appears to be a reliable test for diagnosing *Helicobacter pylori* infection.

The results obtained in the three studies (N=441) conducted with the 5‰ positivity threshold recommended for HELI-KIT® were as follows:

- the sensitivity of the ^{13}C UBT was between 96.5% and 98.6%
- its specificity was between 97% and 98.3%
- its accuracy was between 97.0% and 98.5%.

In addition, the performance of the ^{13}C UBT did not depend on the type of equipment used to measure ^{13}C urea in exhaled air (IRMS, NDIRS or laser analyser) [Savarino 1999, Savarino 2000].

3.1.2. Comparative data

3.1.2.1. Performance of the ^{13}C UBT compared to other non-invasive methods used to diagnose *Helicobacter pylori*

One of the nine studies analysed [Monteiro 2001] compared the ^{13}C UBT to three other non-invasive tests used to diagnose *Helicobacter pylori* infection (HpSA, ELISA serology and immunoblot serology). The results are presented in table 2.

Table 2: Performance of the ^{13}C UBT (75 mg of ^{13}C urea, measurement after 30 min, threshold 3.5‰) compared to the three other non-invasive tests used to diagnose Helicobacter pylori infection [Monteiro et al 2001]

	Sensitivity %	Specificity %	PV+ %	PV- %
Culture	100 (95% CI:96.3-100)	100 (95% CI:96.3-100)	100	100
UBT	**93.3 (95% CI:88.4-98.2)**	**98.1 (95% CI:95.5-100)**	**97.7**	**94.6**
Serology (ELISA)	95.6 (95% CI:91.5-99.6)	92.6 (95% CI:87.4-97.8)	91.5	96.2
Serology (immunoblot)	95.6 (95% CI:91.5-99.6)	92.6 (95% CI:87.4-97.8)	91.5	96.2
HpSA	88.9 (95% CI:82.7-95.1)	94.4 (95% CI:84.6-98.8)	90.9	90.7

The results do not show any statistically significant difference between the various tests in terms of diagnostic performance (p>0.05).

3.1.2.2. Performance of HELI-KIT® compared to other ^{13}C UBTs approved in France for *in-vivo* diagnosis of *Helicobacter pylori* infection

Table 3 presents the sensitivity and specificity data in adults of the three other ^{13}C UBTs approved in France for *in-vivo* diagnosis of *Helicobacter pylori* infection.

Table 3: Comparison of performances of the four ^{13}C UBTs assessed in the initial diagnosis of Helicobacter pylori infection in adults (benchmark method: culture and/or histology)

	Sensitivity %	Specificity %
^{13}C UBT conducted according to the methods recommended for HELI-KIT® (N =441)	96.5-98.6	97-98.3
Helicobacter test INFAI (N=457)[10]	96.5-97.9 IC 95% : 94.05-99-72	96.7-100 IC 95% : 94.2-103.7
PYLOBACTELL (N=100)[11]	>95	91.3%-94.3
UBIT (N=248)[12,13]	98 versus culture and histology	78.8 versus culture and 83.3 versus histology

The sensitivity and specificity results of the ^{13}C UBT conducted according to the method recommended in the HELI-KIT® SPC suggest that its efficacy is similar to that of the three other ^{13}C UBTs approved for *in-vivo* diagnosis of *Helicobacter pylori* infection. However, a direct comparative study would be useful to allow conclusions to be drawn.

[10] Source : Helicobacter test INFAI SPC
[11] Source : EPAR PYLOBACELL – Scientific discussion
[12] Transparency Committee's opinion dated 1 September 2004
[13] OHARA S et al. Studies of 13C-urea breath test for diagnosis of *Helicobacter pylori* infection in Japan. *J Gastroenterol. 1998;33:6-13.*

3.2. Adverse effects / Safety

The tolerance of ^{13}C UBT conducted by administering 75 mg of ^{13}C urea with citric acid was assessed in two of the nine studies, involving 722 patients of whom 230 had received 2.4 g of citric acid [d'Elios 2000, Wong 2000]. Only one adverse event was reported: moderate abdominal pain occurring 20 minutes after administration of the mixture (the dose of citric acid was not specified). No adverse events were reported in the 202 patients who received 2.4 g of citric acid.

It should be remembered that the dosage recommended by the SPC is 75 mg of ^{13}C urea and 1.4 g of citric acid.

Furthermore, periodic safety update reports (PSURs) indicate that no adverse event has been reported in association with HELI-KIT® since it was first introduced on the market (February 2002).

3.3. Conclusion

An analysis of the results of nine clinical studies conducted in the initial diagnosis of *Helicobacter pylori* infection in 1,787 adults with dyspepsia according to methods identical or similar to those recommended for HELI-KIT® shows good reliability of the test in this indication, with a sensitivity ranging from 93.3 to 100 (median value 98%), specificity ranging from 97 to 100% (median value: 98.5%) and median accuracy of 98%. These characteristics were obtained with reference to the standard diagnostic method: endoscopy with identification of the bacteria by culture and/or histology and rapid urease test.

Furthermore, although no direct comparison is available, the reliability of HELI-KIT® can be considered similar to that of the three other ^{13}C UBTs approved in France for the *in-vivo* diagnosis of *Helicobacter pylori infection*.

HELI-KIT® is very well tolerated. No adverse effect has been reported.

4 CONCLUSIONS OF THE TRANSPARENCY COMMITTEE

4.1. Actual benefit

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

This product is used for diagnostic purposes.

The efficacy/safety ratio is high.

This proprietary drug is a first-line product in patients for whom a non-invasive diagnostic method is appropriate as an initial step (see paragraph 4.3).

There are invasive and non-invasive diagnostic alternatives to this product.

> In terms of public health, the burden represented by complications of *Helicobacter pylori* infection is probably moderate. But the number of patients unable to undergo fibroscopy in the first instance is small, and therefore the burden resulting from the relevant patients for that indication is low.
>
> It is unclear how many complications would be avoided by a urea test of this type. HELI-KIT® is a test that produces a reliable diagnosis. But as gastric fibroscopy is still recommended in France as a first-line procedure, the expected public health benefit of this proprietary product relates only to this sub-population of patients, and, as with other urea tests, the expected benefit should be small.
>
> This public health benefit will have to be revised if there are any changes to French recommendations.

The actual benefit is substantial.

4.2. Improvement in actual benefit

In this extended indication, HELI-KIT® does not provide any improvement in actual benefit (IAB V) compared to the other ^{13}C labelled urea breath tests which are available.

4.3. Therapeutic use

^{13}C UBTs are reliable tests for both the initial diagnosis and monitoring of *Helicobacter pylori* eradication.
In *in-vivo* diagnosis of *Helicobacter pylori* infection, available recommendations[14,15] state that endoscopy plus biopsy should be the first method employed to diagnose the infection, and

[14] CANARD J.M. et al. Recommendations de la SFED [French Society of Digestive Endoscopy recommendations]. Places respectives de l'endoscopie et du test respiratoire dans le diagnostic et le contrôle de l'éradication d' *Helicobacter pylori*. [Respective places of endoscopy and breath test in diagnosing and monitoring the eradication of *Helicobacter pylori.* September 2003.
[15] Conférence de consensus *Helicobacter pylori* Révision 99. Conclusions et recommandations révisées du groupe de travail. [Consensus-building conference Helicobacter pylori Revision 99. Revised conclusions and recommendations of the working group]. *Gastroenterol Clin Biol 1999 ; 23 : C95-C104*

that the urea breath test should be used only 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. However, there are clinical situations which can justify the use of a non-invasive method right from the start, in particular:

- if performance of biopsies are contraindicated (patient on anticoagulant treatment),
- where an endoscopy has been performed but there is still some doubt as to whether *Helicobacter pylori infection* is present (in particular, with biopsies performed while the patient was on anti-secretory treatment),
- to ascertain whether a first-degree relative of a person with gastric cancer has an *Helicobacter pylori* infection,
- when a patient refuses to undergo endoscopy.

In France, ^{13}C UBTs are recommended only to monitor *Helicobacter pylori* eradication when endoscopy is not necessary[14,15]. The test must be performed four to six weeks after the end of anti-secretory or antibiotic treatment.

4.4. Target population

French recommendations advise the test to be used in the monitoring of *Helicobacter pylori* eradication. It is estimated that 60,000 to 80,000 new cases of duodenal ulcer and 15,000 to 20,000 new cases of gastric ulcer are diagnosed every year. It is also thought that 90% of patients with a duodenal ulcer and 70% of patients with a gastric ulcer are infected with *Helicobacter pylori*[16]. In total, **64,500 to 86,000 new patients** a year could benefit from a ^{13}C-labelled urea breath test.

We do not have any data relating to the practical use of the test in primary diagnosis of *Helicobacter pylori* infection. The number of patients is very likely to be low. In the light of the current official French recommendations, it does not seem appropriate to increase the estimate of the number of patients likely to benefit from a ^{13}C UBT.

4.5. Transparency Committee recommendations

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 in the extension of indication.

Packaging: Appropriate for the conditions of prescription.

Reimbursement rate: 65%

[16] AFSSAPS [French Health Products Safety Agency] – RBP [Good Practice Recommendations]– Les antiulcéreux chez l'adulte [Anti-ulcer products in adults]- Revision 99.