HELICOBACTER TEST INFAI for children aged 3 to 11 45 mg, powder for oral solution B/1 with diagnostic kit (CiP code: 383 086-0)

Applicant: INFAI

$^{13}$C urea (45 mg)
ATC code (2008): V04CX

List I

Date of Marketing Authorisation: 10 October 2002

Reason for request: Inclusion on the list of medicines refundable by National Health Insurance and approved for hospital use.
1. CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient

$^{13}$C urea

1.2. Indication(s)

"Helicobacter Test INFAI may be used for in vivo diagnosis of gastroduodenal Helicobacter pylori infection in children aged 3 to 11
- to assess the efficacy of suppression treatment, or
- when invasive examinations cannot be performed, or
- when the results of invasive examinations conflict with each other.
This medicinal product is for diagnostic use only."

1.3. Dosage

"Helicobacter Test INFAI for children aged 3 to 11 is a breath test for single administration. The dosage for patients aged between 3 and 11 is one 45-mg jar.
This medicinal product must be administered by a healthcare professional under appropriate medical supervision.
For the performance of the test, the patient must swallow 100 ml of pure orange juice (100% concentrate) as a test meal before the test and tap water (for dissolving the 13C-urea).
The patient must have fasted for over 6 hours, preferably overnight. The test procedure takes approximately 40 minutes.
In case it is necessary to repeat the test procedure, this should not be done until the following day.
The suppression of Helicobacter pylori might give false negative results. Therefore the test shall be used after at least four weeks without systemic antibacterial therapy and two weeks after last dose of acid antisecretory agents. Both might interfere with the Helicobacter pylori status. This is especially important after Helicobacter eradication therapy.
It is important to follow the instructions for use adequately (see section 6.6), otherwise the reliability of the outcome will become questionable."

2. SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification (2009)

V: Various
V04: Diagnostic agents
V04CX: Other diagnostic agents

2.2. Medicines in the same therapeutic category

2.2.1 Strictly comparable diagnostic agents

No other breath test based on $^{13}$C urea is indicated for children aged 3 to 11.
2.2.2 Diagnostic agents that are not strictly comparable

Other tests based on $^{13}$C urea:

<table>
<thead>
<tr>
<th>Proprietary product</th>
<th>Pharmaceutical form</th>
<th>On the market</th>
<th>Indication (Authorised age)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HELICOBACTER TEST INFAI 75 mg</td>
<td>Powder for oral solution</td>
<td>Yes</td>
<td>“Helicobacter Test INFAI can be used for in-vivo diagnosis of gastroduodenal infection involving <em>Helicobacter pylori</em> in: - adults  - adolescents who might have a peptic ulcer.” (adolescents from 13 to 17 and adults)</td>
</tr>
<tr>
<td>HELIKIT 75 mg</td>
<td>Powder for oral suspension</td>
<td>yes</td>
<td>“<em>In-vivo diagnosis of Helicobacter pylori</em> infection, particularly monitoring its eradication. See the official recommendations for the treatment of <em>Helicobacter pylori</em> infections.” (adults)</td>
</tr>
<tr>
<td>UBIT 100 mg</td>
<td>Film-coated tablet</td>
<td>yes</td>
<td>“UBIT is indicated for in-vivo diagnosis of <em>Helicobacter pylori</em> gastroduodenal infection.” (adults)</td>
</tr>
<tr>
<td></td>
<td>Granules for oral solution in single-dose sachets</td>
<td>no</td>
<td></td>
</tr>
</tbody>
</table>

2.3. Other methods of diagnosis

- non-invasive tests:
  - serology
  - faecal antigen test
- invasive tests:
  - endoscopy with biopsy: rapid urease test, histological examination, PCR, bacterial culture.
3. ANALYSIS OF AVAILABLE DATA

The company submitted seven clinical studies. Only one of these studies (UR98/2/001) involved administration of 45 mg of $^{13}$C urea to children aged 2 to 11 and produced efficacy results specifically for this age group. Consequently, this is the only study taken into account for efficacy analysis.

3.1. Efficacy: study UR98/2/001

Two groups of patients were included in this study:

- children aged 2 to 11 who were given the 45-mg dose
- adolescents aged 12 to 17 who were given the 75-mg dose

Only the results for children aged 2 to 11 are presented.

3.1.1 Method

- Open-label prospective study
- Inclusion criteria: children aged 2 to 11 for whom upper digestive endoscopy and testing for *H. pylori* were indicated
- Administration of a single dose of 45 mg of $^{13}$C urea. The $^{13}$CO$_2$/^{12}$CO$_2$ ratio was measured before administration and 30 min after administration. The test was regarded as positive if the difference between these two values exceeded 4‰.
- Primary efficacy endpoints: sensitivity, specificity, positive and negative predictive values of the $^{13}$C urea breath test and their one-sided 90% confidence interval (CI).
  
  **Reference method:** culture + histology + rapid urease test:
  - True positive: culture and/or histology + rapid urease test positive
  - True negative: culture negative + histology negative or culture negative + urease test negative or culture impossible to assess + histology negative + urease test negative.

- Secondary endpoints:
  - Sensitivity and specificity of other non-invasive tests: faecal antigen test (PREMIER, Meridian) and serology test (PYLORISET EIA, Orion Diagnostica)
  - Calculation of the ROC curve of the $^{13}$C urea test.

3.1.2 Result:

- Two hundred and four children were included, 180 of whom were included in the efficacy analysis (results available for the reference method and for HELICOBACTER PYLORI TEST INFAI 45 mg).
- According to the reference method, *H. pylori* was diagnosed in 63 out of the 180 children who could be assessed, i.e. 35%.
- Primary efficacy endpoints:
  - Sensitivity: 96.8% (61/63) [CI: ≥ 91.8%]
  - Specificity: 98.3% (115/117) [CI: ≥ 95.5%]
  - PPV: 96.8 % (61/63) [CI: ≥ 91.8%]
  - NPV: 98.3 % (115/117) [CI: ≥ 95.5%]
- Two false positives (2/117, 1.7%) were observed in three-year-old children.
- According to the ROC curve, the value of the threshold > 4‰ is the one which has the best performance$^1$.

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$^1$ EPAR for HELICOBACTER TEST INFAI:  
3.2. Adverse effects
No adverse effect was noted during the study, and the EPAR\(^1\) states that none was expected.

3.3. Conclusion
The EPAR\(^1\) concludes that diagnostic performance in children was comparable to that observed in adults and adolescents, and that this test does not give rise to any tolerance problems.

4. TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit
- *Helicobacter pylori* infection causes chronic gastritis and, more rarely, gastric or duodenal ulcers.
- The proprietary product is a diagnostic test.
- The efficacy (diagnostic performance)/adverse effects ratio is high.
- Public health benefit:
  - The burden which complications of *Helicobacter pylori* infection (gastroduodenal ulcer) present is small in children (as the condition is rare in this age group). The burden corresponding to the population for which the diagnostic indication of HELICOBACTER TEST INFAI is relevant is therefore small.
  - Diagnosing *Helicobacter pylori* in children is not a public health need that is part of established priorities.
  - The data available does not provide any information as to what morbidity would be avoided if *Helicobacter pylori* could be diagnosed in the population for which the indication is relevant.
  - The HELICOBACTER TEST INFAI test could have a positive impact on the organisation of the health system (no need for endoscopy to check the diagnosis, simpler management of patients with *Helicobacter pylori* infection) provided that it is used appropriately. This impact could actually be reduced if the test is performed as a first-line procedure before endoscopy and if endoscopy is not contraindicated.
  - Consequently, the public health benefit of the proprietary product HELICOBACTER TEST INFAI can only be minor.
- Therapeutic use: this proprietary product is a second-line diagnostic test after fibroscopy with invasive tests.
- Alternative procedures exist (serology, faecal antigen test).
- The actual benefit of this proprietary medicinal product is substantial.

4.2. Improvement in actual benefit (IAB)
HELICOBACTER TEST INFAI 45 mg provides a minor improvement in actual benefit (IAB IV) in the diagnostic strategy of ascertaining *Helicobacter pylori* infection in children aged 3 to 11 in the indications in the marketing authorisation.
4.3. Therapeutic use

4.3.1 Diagnostic strategy

A European consensus-building conference\(^2\) specifies that “recurrent abdominal pain is not an indication for testing for \textit{H. pylori} in children. The main objective of diagnostic investigations in cases of recurrent abdominal pain is to ascertain their cause, not to look for \textit{H. pylori} infection. However, tests for \textit{H. pylori} must be performed in children who have upper digestive tract symptoms once other causes have been ruled out”.

4.3.2 Diagnostic use

The EPAR\(^1\) states that the prevalence of \textit{H. pylori} is low in European children and those peptic ulcers and other pathologies associated with \textit{H. pylori} in adults rarely affect children. In addition, the indications for eradication treatment in children with \textit{H. pylori} infection have not been clearly established. Consequently, the risk/benefit ratios of performing diagnostic tests and treatments for \textit{H. pylori} are different in adults and in children. It is not recommended that tests be carried out on children as a first-line procedure. This may compromise the optimum management of this group of patients by exposing them to the risk of inappropriate antibiotic prescription. Upper digestive tract endoscopy with biopsies remains the preferred method of diagnosis for children with chronic upper digestive tract symptoms. Breath tests with urea\(^{13}\)C should not therefore be an alternative to upper digestive tract endoscopy for the primary diagnosis of \textit{H. pylori} infection in children. Consequently, this test is indicated for children where invasive tests cannot be carried out, where the results of such tests are inconclusive or to monitor the efficacy of eradication treatment.

4.4. Target population

In France, the rate of \textit{H. pylori} infection among children varies from 5 to 10% according to age. Infection rarely occurs below age 4, and its prevalence increases with age\(^3\). Data from the PMSI (public and private basis) indicates that 304 “oesogastroduodenal endoscopies with urease testing below age 6” were performed in 2007. As this number is a third of all oesogastroduodenal endoscopies with urease testing that were performed on children aged 3 to 11, it is estimated that 920 such procedures were carried out on children aged 3 to 11 in 2007.

The target population for HELICOBACTER TEST INFAI 45 mg includes:

- children producing a positive result in the urease test who are undergoing examination to ascertain the success of eradication. The rate of \textit{H. pylori} infection among children who underwent this diagnostic procedure is estimated at 42% (high estimate)\(^4\);
- children in whom the results of the endoscopy with urease testing are inconclusive. In study UR98, the results of the reference method were not available for 24 out of the 204 children who took part, or 12% of the children who were eligible for an endoscopy.
- children on whom an endoscopy with urease testing cannot be performed. The proportion of children affected is unknown.

This information indicates that the target population for HELICOBACTER TEST INFAI would be around 950 children aged 3 to 11.


4.5. **Transparency Committee recommendations**

The transparency Committee recommends 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 in the indication and at the posology in the marketing authorisation.

4.5.1 **Packaging:** Appropriate for the prescription conditions

4.5.2 **Reimbursement rate:** 65%

4.5.3 **Additional information requested from the pharmaceutical company:**

The Committee requests that a study be set up to examine the following aspects under actual conditions of use of the test:
- the characteristics of the children (age, gender, medical history, especially of gastric disorders, related and prior treatments, prior examinations, in particular the results of any endoscopy, etc.);
- the characteristics of the prescribing physician (discipline, practice type, etc.);
- the circumstances under which the test was prescribed, in particular a description of the clinical and diagnostic criteria justifying its conduct (monitoring eradication, primary diagnosis if endoscopy is contraindicated, other factors, etc.) and, where applicable, the reasons why endoscopy is contraindicated;
- the proportion of children with or without *Helicobacter pylori* infection, analysing specifically the rate of infection according to the indication;
- the consequences of the test in terms of management (new endoscopy, change in antibiotic treatment, revision of initial diagnosis) in the light of the initial indication;
- the consequences of *Helicobacter pylori* eradication, once it has been achieved, on the digestive symptoms which led to a diagnostic test being performed.

The length of the study, decided on by an independent scientific committee, must be appropriate and sufficient to respond to the Committee’s request. However, the Committee would like to receive results with regard to the characteristics of patients and prescribing physicians and on the circumstances under which the test is prescribed before the end of the study.