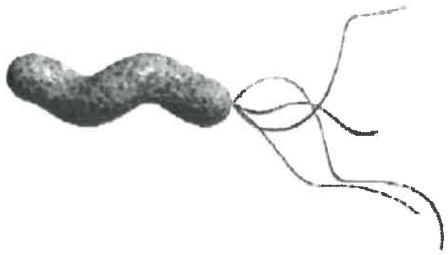
Product Information:

PYtest ®

AUST R 67146

The urea breath test kit

for detecting



Helicobacter pylori

tri-med

Distributed in Malaysia by:

All Eights (M) SDN BHD
45, Jalan TS6/10A,
Subang Industrial Park
47610 Subang Jaya,
Selangor Darul Ehsan
Malaysia
Tel: (603) 5633 4988 Fax: (603) 5633 0261

PYTEST® KIT (UREA[^{14}C] BREATH TEST)

Description

PYtest® (urea[^{14}C] breath test) is a qualitative and non-invasive method for the diagnosis of *Helicobacter pylori* (*H.pylori*). To detect *H.pylori*, urea[^{14}C] supplied in a capsule is swallowed by the patient. If gastric urease from *H.pylori* is present, urea is split to form CO_2 and NH_3. Ten minutes after the patient ingests the capsule a breath sample is collected into a balloon. The breath sample is later transferred to collection fluid to trap the labelled CO_2. The liquid sample is then analysed in a liquid scintillation counter.

The PYtest® Kit (urea[^{14}C] breath test) is designed for use with the PYtest® capsule, a gelatin capsule for oral administration containing 37 kBq (±20%) of ^{14}C labelled urea. The urea is adsorbed on sugar spheres and coloured yellow with fluorescein.

Composition:

A gelatin capsule contains:

0.2 g (±20%) sugar spheres containing sucrose and maize starch

7.0 µg (±20%) fluorescein sodium

1 µg Urea [^{14}C] (37 kBq ^{14}C) (±20%)

Structural Formula: (Urea [^{14}C]): NH2 ^{14}CONH2

Physical Characteristics of ^{14}C

Radiation emission: beta-emission, 49 keVmean, 156 keVmax, no other emissions

External emission: No external radiation hazard. Low-energy beta emissions only. Maximum range of 0.3 mm in water.

Physical Half-life: 5730 years

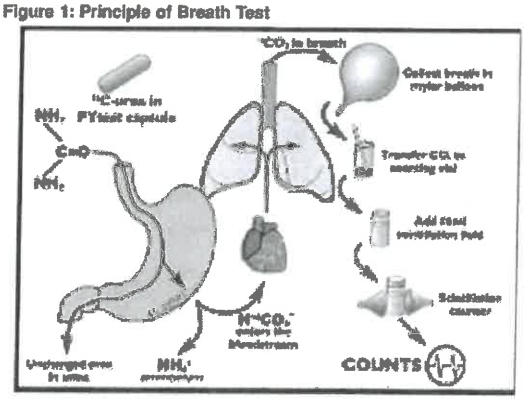
Radiation Dosimetry

Maximum effective dose (ED) (*H.pylori* positive): 3 µSv /37kBq

Clinical Pharmacology

The urease enzyme is not present in mammalian cells, so the presence of urease in the stomach is evidence that bacteria are present. The presence of urease is not specific for *H.pylori*, but other bacteria are not usually found in the stomach. The principle of the breath test is shown in Figure 1.

Figure 1: Principle of Breath Test



To detect *H.pylori*, urea labeled with ^{14}C is swallowed by the patient. If gastric urease from *H.pylori* is present, urea is split to form CO_2 and NH_3 at the interface between the gastric epithelium and lumen and $^{14}CO_2$ is absorbed into the blood and exhaled in the breath.

Following ingestion of the capsule by a patient with *H.pylori*, $^{14}CO_2$ excretion in the breath peaks between 10 and 15 minutes and declines thereafter with a biological half-life of about 15 minutes. Urea[^{14}C] that is not hydrolysed by *H.pylori* is excreted in the urine with a half-life of approximately 12 hours. About 10% of the ^{14}C remains in the body at 72 hours and is gradually excreted with a biological half-life of 40 days.

Clinical Studies

Two studies were performed. In both studies, patients with gastrointestinal symptoms underwent the breath test and an endoscopy. During the endoscopy, biopsy samples were taken from the antral gastric mucosa for histological analysis (2 samples, Giemsa stain) and rapid urease test (1 sample, CLOtest®). Breath samples were mailed to a laboratory where they were read in a liquid scintillation counter. Results were reported as disintegrations per minute (DPM). Analysis for accuracy used the ten minute breath sample. A breath sample DPM <50 was defined as a negative result. DPM ≥200 was defined as a positive result. DPM in the range of 50 -199 was classified as indeterminate.

STUDY 1:

Of 186 patients who had histopathology and Campylobacter Like Organism [(CLO)test®] (80 men, 106 women), 53 were infected with *H.pylori* as determined by agreement between histology and CLOtest®. The study results are summarized below

Table 1: Study #1 (n=186, Indeterminate results included)

		Histology and CLOtest®			
	H.pylori	Positive	Negative	Total	
PYtest® (DPM 10mins.)	Positive	51	8	59	ppv.86%
	Indeterminate	1	8	9	
	Negative	1	117	118	npv.99%
	Total	53	133	186	
		sensitivity 96%	specificity 88%		

Notes: PYtest® at 10 min. was compared to the gold standard of biopsy results in which histology and CLOtest® concurred. Patients who did not have both biopsy tests performed, or in whom the tests differed, were excluded from analysis. There was no statistical difference in test accuracy based on gender of patient.

ppv = positive predictive value (total PYtest® positive divided by true positive)

npv = negative predictive value (total PYtest® negative divided by true negative)

STUDY 2:

Breath tests were performed on seventy-six patients (40 men, 36 women) who had histology and CLOtest performed also. The results are summarized below:

Table 2: Study #2 (n=76, Indeterminate results included)

		Histology and CLOtest®			
	H.pylori	Positive	Negative	Total	
PYtest® (DPM 10mins)	Positive	22	0	22	ppv.100%
	Indeterminate	4	2	6	
	Negative	1	47	48	npv.98%
	Total	27	49	76	
		sensitivity 82%	specificity 96%		

Notes: PYtest® at 10 min. was compared to the gold standard of biopsy results in which histology and CLOtest® concurred. Patients who did not have both biopsy tests performed, or in whom the tests differed, were excluded from analysis. There was no statistical difference in test accuracy based on gender of patient.

ppv = positive predictive value (total PYtest® positive divided by true positive)

npv = negative predictive value (total PYtest® negative divided by true negative)

Table 3: Summary of Accuracy

	Study 1	Study 2
Sensitivity (95% CI)*		
Including Indeterminates	0.96 (0.87,1.00)	0.82 (0.62,0.94)
Excluding Indeterminates	0.98 (0.90,1.00)	0.96 (0.78,1.00)
Specificity (95% CI)*		
Including Indeterminates	0.88 (0.81,0.93)	0.96 (0.86,1.00)
Excluding Indeterminates	0.94 (0.88,0.97)	1.00 (0.93,1.00)
Predictive Values (95% CI)*		
Positive Predictive Value	0.86 (0.75,0.94)	1.00 (0.85,1.00)
Negative Predictive Value	0.99 (0.95,1.00)	0.98 (0.91,1.00)

Values in parentheses are 95% confidence intervals determined by using an exact procedure for binomial proportions.

Indications and Usage

PYtest® (urea[^{14}C] breath test) is indicated for use in the detection of gastric urease as an aid in the diagnosis of *H.pylori* infection in the human stomach.

Precautions

General: After the patient ingests the urea[^{14}C] capsule, the sample collected for test purposes is for in vitro diagnostic use only.

A false positive test could occur in patients who have achlorhydria. Very rarely, a false positive test may occur due to urease associated with Helicobacters other than *H.pylori* (e.g. *Helicobacter heilmanii*).

Limitations of the Test:

- The test has been evaluated in outpatients before elective endoscopy.
- Test results should be considered together with clinical signs and patient history when diagnosing *H.pylori* infection.
- A negative result does not completely rule out the possibility of *H.pylori* infection. If clinical signs and patient history suggest *H.pylori* infection, repeat the PYtest® or use an alternative diagnostic method.

Information for Patients:

It is necessary for the patient to fast for 4 hours before the test. The patient should not have taken antibiotics or bismuth containing products for 1 month, sucralfate for 2 weeks and proton pump inhibitors for 1 week prior to the test. Instruct the patient not to handle the capsule directly as this may interfere with the test result. The capsule should be swallowed intact. The capsule should not be chewed.

Carcinogenesis, mutagenesis, impairment of fertility: No studies have been conducted with urea[^{14}C] to evaluate its potential for carcinogenicity, impairment of fertility, or mutagenicity.

Drug Interactions: Antibiotics, proton pump inhibitors, sucralfate, and bismuth containing drug preparations are known to suppress *H.pylori*. Ingestion of antibiotics or bismuth within 4 weeks, sucralfate within 2 weeks or proton pump inhibitors within 1 week prior to performing the test may give false negative results.

Pregnancy:

Animal reproduction studies have not been conducted with PYtest® (urea[^{14}C]). It is also not known whether PYtest® can cause foetal harm when administered to a pregnant woman or can affect reproduction capacity. When administration of PYtest® to a woman of child bearing potential is considered, information should always be sought about pregnancy.

Nursing mothers: It is not known whether this drug is excreted in human milk.

Paediatric Use: Clinical studies in children have not been conducted.

Post Treatment Evaluation: A negative PYtest 28 days after completing antibiotic treatment is evidence that the infection has been eradicated.

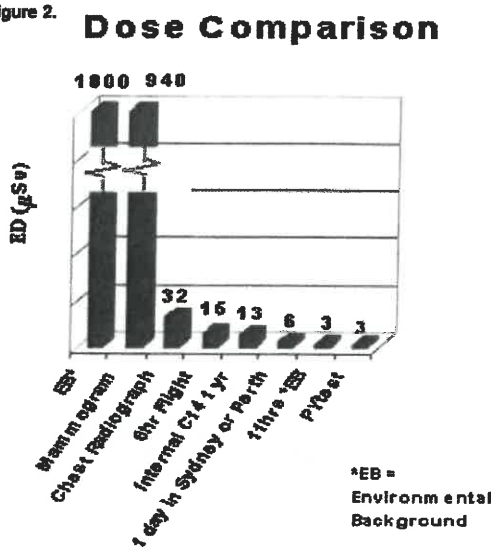
Radiation Safety

To allow radiation sources to be effectively compared emissions of various origins are expressed in terms of "effective dose" (ED). The ED of ^{14}C takes into account the fraction of isotope sequestered in each organ tissue (as recommended by the International Commission for Radiological Protection 60 [ICRP-60] which is adopted in Australia), the biological half life of the isotope in that tissue, the effective energy of the beta particles compared with standard ionising radiation (200kV x-ray source) and the administered dose. ED is expressed in Sieverts (1 Sievert [Sv]; 10^{-6} Sv = 1μSv).

The maximum estimated ED received from a single administration of PYtest® capsule (37kBq of [^{14}C]-urea) is 3 μSv; Figure 2 summarizes radiation exposure from the PYtest® in comparison with other common sources of radiation exposure.

The Australian population is subjected to an annual radiation dose of about 1800μSv to 2400μSv per caput as a result of natural environmental radiation and the in vivo presence of radionuclides such as natural ^{14}C and ^{40}K in the body. 2400μSv is equivalent to the radiation dose afforded by the ingestion of 800 PYtest® capsules. A single PYtest® procedure is the equivalent of about 11 hours of normal and essentially inevitable radiation exposure from the environment.

Figure 2.



Adverse Reactions

There were no adverse reactions reported in clinical trials at a rate > 1%. All adverse reactions reported were felt by the investigators to be unrelated to the PYtest®.

Any suspected adverse reaction should be reported to:

Therapeutic Goods Administration
Office of Product Review
PO Box 100
Woden, ACT 2606
Australia
Fax: 02 6232 8392 OR report via email using a Blue card.

Overdosage

In the event of overdose, the patient should drink one glass of water (150 mL) every hour to hasten excretion of the radioisotope. Maximum excretion of urea is achieved at a urine output of ≥2.0mL/min.

Dosage and Administration

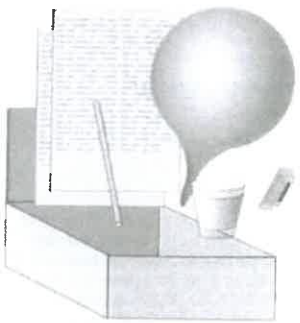
Materials provided:

As shown in Figure 3, the PYtest® Kit contains:

- PYtest® capsule
- Two 30 mL disposable cups
- One drinking straw
- One Pioneer brand biax balloon
- One report form
- One mailing box with labels**

** The kit includes analysis by TRI-MED Distributors, Pty Ltd of one balloon from one patient at one time point.

FIGURE 3. PYTEST® KIT



Materials Needed but not Provided:

1.Stopwatch/Timer capable of timing an interval up to 10 minutes.
2.Water (40mL)

Dosage:

One PYtest® capsule.

Procedural Notes:

- Inform the patient to fast for 4 hours prior to the test.
- The patient should not have taken antibiotics and bismuth containing products for 1 month, proton pump inhibitors for 1 week and sucralfate for 2 week prior to the test.
- Have patient sitting at rest while doing the test.
- The capsule should not be handled directly as this may interfere with the test result.
- To avoid contamination by bacteria in the mouth, the capsule should be swallowed intact. Do not chew capsule.

Step by Step Procedure for Balloon:

Table 4: Breath Sample Collection by Balloon

Before the test	1. Label balloon and fill in breath test report form. 2. Check that all materials are present.
Minus 1 minute	1. Open the package containing the PYtest® capsule and tip the capsule into the empty 30 mL cup. Do not handle the capsule directly. 2. Hand the cup to the patient. 3. Fill the second cup with 20 mL lukewarm water.
0 minute	1. Ask the patient to tip the capsule directly into his/her mouth, then swallow it with the 20 mL of lukewarm water. 2. Start the stopwatch when the patient swallows the capsule. 3. Discard waste (e.g., capsule packaging, used straws) according to your facility's regulations.
3 minutes	Ask the patient to drink another 20 mL of lukewarm water (in case the capsule may have lodged in the oesophagus and not yet reached the gastric mucosa).
10 minutes	1. Push a drinking straw into the neck of the balloon. 2. Ask the patient to hold his/her breath for 5-10 seconds, then blow up a balloon with a slow breath through the straw, filling the balloon completely. 3. Tie the neck of the balloon into a tight knot. 4. Check that the balloon label and the breath test report form are completed correctly.
After the test	Place the filled balloon and breath test report in the box and forward to TRI-MED Distributors Pty Ltd, at Unit 6, 15 Walters Drive, Osborne Park, WA 6017.

Precautions for Use

Because of the very low radioactivity of individual PYtest® capsules, no special precautions are needed for the disposal of small numbers of capsules. Where it is necessary to dispose large quantities of capsules, the disposal of the waste should be carried out in accordance with the NHMRC Code of Practice for the Disposal of Radioactive Waste by Users, (1985).

Quality Control

A minimum of 1 mmol of CO_2 is required to perform analysis of a breath sample. The amount of breath required to provide 1 mmol of CO_2 varies depending on the amount of CO_2 the patient is producing. Since a full balloon typically contains at least 1 mmol of CO_2, the balloon should be completely filled.

RESULTS

Interpretation of results (10 minute sample)

<50 DPM	Negative for *H.pylori*
50-199 DPM	Borderline Positive for *H.pylori*
>200 DPM	Positive for *H.pylori*

(DPM = disintegrations per minute)

Borderline positive result should be evaluated by repeating the PYtest® or using an alternative diagnostic method. If repeat breath testing is undertaken, careful history to exclude confounding factors should be obtained. If confounding factors are present, wait an appropriate time (refer to Table 5) before repeating the PYtest®.The cutoff point of 50 DPM was determined to be the mean + 3SD of results obtained in-patients who did not have *H.pylori*.

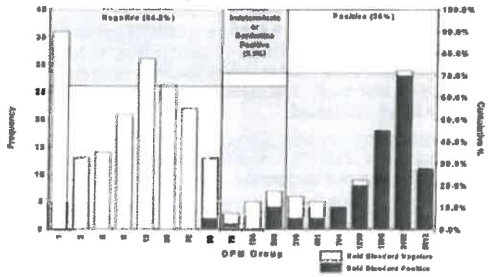
Table 5: Confounding Factors

Factor	Result	Comment
Recent antibiotic or bismuth containing products	False neg.	Relapse of partially treated *Helicobacter pylori (Hp)* may take 1-4 weeks.
Omeprazole (or other proton pump inhibitors)	False neg.	These agents suppress *Hp* in 40% of patients. Discontinue for at least 1 week before performing the PYtest.
Sucralfate	False neg.	This agent suppresses *Hp*
Resective gastric surgery	False neg.	Isotope may empty rapidly from the stomach.
Resective gastric surgery	False pos.	Patient may be achlorhydric and have bacterial overgrowth (non-*Hp* urease).
Food in stomach (also bezoar, gastroparesis)	Unknown	Isotope may not come into contact with gastric mucosa. Patient may be achlorhydric and/or have bacterial overgrowth (non-*Hp* urease).

Expected Values

As shown in Figure 4 approximately 30% of patients tested will be positive for *H.pylori*.

Figure 4: Histogram showing DPM distribution for the PYtest®



*Note: DPM groupings were calculated on a logarithmic scale. Empty DPM groupings were not included. Chart includes all patients from Studies 1 and 2. Frequency of DPM group includes samples with DPM < Group Name.

DPM = Disintegrations per minute
Gold Standard = Agreement between histology and CLOtest

If the capsule is damaged or appears abnormal in any way, it may give inaccurate results.

How Supplied

PYtest® kit (urea [^{14}C] breath test) is supplied as a kit containing a PYtest® capsule; a clear gelatin capsule containing 37 kBq of urea [^{14}C] and breath collection accessories.

PYtest® capsules are also supplied separately in unit dose packages of 1, 10 and 100.

The PYtest® capsule has a shelf life of three years.The expiration date is printed on the capsule label.

PYtest® capsules and kit should be stored below 30°C in an area designated by each individual institution's regulations.

Manufactured by: AVENT, Inc.
6620S. Memorial Place,
Suite 100, Tucson, AZ 85756,
United States of America

Distributed in Malaysia by:

All Eights (M) SDN BHD
45, Jalan TS6/10A,
Subang Industrial Park
47610 Subang Jaya,
Selangor Darul Ehsan
Malaysia
Tel: (603) 5633 4988 Fax: (603) 5633 0261

THE PYTEST HAS BEEN APPROVED BY THE THERAPEUTIC GOODS ADMINISTRATION ON THE 27TH OF NOVEMBER 1998. AUST R 67146

Jun 2020

PI1.8.1

MSIA NOV 2020