-DIAGNOSTIC AGENT for *Helicobacter Pylori* Infection-

UBIT® tablet 100mg

< Urea (13C) preparation >

COMPOSITION AND DESCRIPTION

1. Composition
   Each tablet 100mg contains 100 mg of urea (^{13}C) and the following inactive ingredients: lactose, microcrystalline cellulose, corn starch, magnesium stearate, hydroxypropylmethylcellulose, macrogol 6000, talc and titanium oxide.

2. **Product description**
   UBIT tablet 100mg is white film-coated tablets.

Appearance	Diameter (mm)	Thickness (mm)	Weight (mg)	Code
	8.1	3.7	Approx. 204	OG73

INDICATIONS

In vivo diagnosis of *Helicobacter pylori (H. pylori)* infection.

CONTRAINDICATIONS

Patients with a known hypersensitivity to the product.

DOSAGE AND ADMINISTRATION

Usual adult dosage is one tablet [100mg of urea (^{13}C)] taken orally in a fasting condition.

<Recommended Procedure for ^{13}C-Urea Breath Test>

(1). Collect pre-dose breath sample.
(2). Instruct patient in a fasting condition to promptly (within 5 sec) swallow one **UBIT tablet 100mg** with 100mL of water without crushing or chewing the tablet.
(3). Instruct patient to remain in the left lateral decubitus position for 5 min., and then to return to sitting position until collection of post-dose breath sample.
(4). Collect post-dose breath sample at 20 min. after administration.
(5). Measure $^{13}CO_2$ level (ratio of $^{13}CO_2$ to $^{12}CO_2$) in each breath sample and calculate $\Delta^{13}C$ (difference between pre-dose and post-dose $^{13}CO_2$ levels) for the diagnosis of *H. pylori* infection.

PRECAUTIONS

1. **Adverse Reactions**
   Adverse reactions were reported in 8 (0.7%) of a total of 1,144 patients who received UBIT or **UBIT tablet 100mg** (data available at the time of approval). The following summary of data includes adverse reactions reported after marketing without data on the incidence.

Signs and Symptoms/Incidence	<0.5%	Incidence Unknown*
Hypersensitivity note)		Rash and urticaria
Gastrointestinal	Abdominal distention,diarrhea,and epigastric discomfort	Nausea/Vomiting
Others	Increase in serum potassium level	

Note: If symptoms of hypersensitivity occur, the drug should be discontinued immediately.
*The incidence of adverse reactions reported voluntarily after marketing are not known.

2. Use during Pregnancy, Delivery, or Lactation

The drug should be administered to pregnant, possibly pregnant or lactating women only if the anticipated diagnostic benefit is thought to outweigh any potential risk. (The safety of this drug in pregnant and lactating women has not been established.)

3. Pediatric Use

The safety of this drug in premature babies, newborns, suckling infants, infants, and children has not been established. (There is no clinical experience in these subjects.)

4. Precautions Concerning Use

At time of ingestion: **UBIT tablet 100mg** must be swallowed promptly (within 5 sec.) without being crushed or chewed. (If the tablet disintegrates in the mouth, the diagnostic test result may be influenced by oral bacteria having urease activity, possibly causing a false-positive test result. When **UBIT tablet 100mg** was placed in water, the tablet film coating began to flake in 5-8 sec.)

<Precautions Concerning Diagnosis>

(1). **Diagnostic criteria:** A $\Delta^{13}C$ value of 2.5‰ or higher at 20 min after the administration of one **UBIT tablet 100mg** [100mg of urea (^{13}C)] is considered a positive result for *H. pylori* infection.

(2). $\Delta\,^{13}C$ values for breath samples in the ^{13}C-urea breath test should be determined by mass spectrometry or other appropriate methods with a comparable performance (e.g. infrared spectroscopy). It should be noted that a low CO_2 concentration (<1%) in the expired breath sample may cause poor reproducibility of the measured $\Delta^{13}C$ values, possibly affecting the diagnostic test result at low $\Delta^{13}C$ values.

(3). A false-negative test result may be obtained if the ^{13}C-urea breath test is performed during or immediately after discontinuation of therapy with proton pump inhibitors such as omeprazole, lansoprazole, and sodium rebeprazole, antibiotics such as amoxicillin, clarithromycin, and tetracycline. bismuth preparations, or ecabet sodium preparations having an inhibiting action on gastric urease activity. Assessment of the eradication therapy, when necessary, should be performed at least 4 weeks after termination of the therapy.

(4). False-negative test results were obtained in approx. 2.3% (3 of 130 *H.pylori*-infected subjects) in a Japanese Phase 3 study of **UBIT tablet 100mg**. Result of other tests methods should be used as a reference if patients show a negative test result despite clinical signs or symptoms suggestive of *H. pylori* infection.

(5). Since this drug is a tablet, breath reaction could be delayed by various factors such as passage of the tablet through the stomach without being retained long enough for dissolution, possibly causing a false-negative test result. Therefore, administration of **UBIT tablet 100mg** to patients in whom a

false-negative test result is likely to occur, such as those who have undergone gastrectomy, should be performed carefully.

(6). A false-positive test result may be obtained in patients with achlorhydria or patients who are infected with gastric spiral microorganisms other than *H. pylori* that exhibit urease activity, such as *Helicobacter heilmanii*.

(7). No correlation has yet been established between the bacterial count of *H. pylori* and the ^{13}C-urea breath test result (the measured Δ^{13}C value).

PHARMACOKINETICS

1. Serum concentration of exogenous urea (^{13}C) following single oral administration of 100mg of urea (^{13}C) (UBIT® granules) to 5 healthy adult male volunteers in a fasting condition.

H.pylori antibody titer	T_{max} (hr)	C_{max} (μg/mL)	$t_{1/2}$(hr)	AUC_{0-24hr} (μg.hr/mL)
Positive	0.6±0.2	2.3±0.5	7.7±1.7	21.3±5.4
Negative	1.1±1.1	3.0±0.8	5.7±1.6	24.1±13.4

Mean ± S.D.

Data represent exogenous urea (^{13}C) concentrations determined by subtracting the intrinsic urea (^{13}C) concentration from the measured concentration.

2. Absorption

Almost all of the administered dose was absorbed in rats.

3. Plasma Protein Binding

6.6% in dogs.

4. Major Metabolites and Major Metabolic Pathway

UBIT [urea (^{13}C)] is not metabolized in the body.

5. Excretion Route and Excretion Rate

Excretion route: Renal excretion

Excretion rate: When ^{14}C-urea (51-55 mg as urea) dissolved in 20mL water was administered once orally to 7 non-infected subjects after overnight fasting, the urinary excretion of ^{14}C for 3 days post-dosing accounted for approx. 90% administered dose.

CLINICAL STUDIES

In a Phase 3 study of **UBIT tablet 100mg**, ^{13}C-urea breath test was performed in 130 *H.pylori*-infected patients and 124 non-infected patients diagnosed by a combination of biopsy-based methods (FDA *H.pylori* Infection Assessment Criteria 1995). Based on measurement of $^{13}CO_2$ levels in the expired breath by mass spectrometry employing a cut-off value of 2.5‰ at 20 min. post-dosing. ^{13}C-urea breath test using **UBIT tablet 100mg** showed sensitivity of 97.7% specificity of 98.4%, and accuracy of 98.0%. Comparison of Δ^{13}C values measured by infrared spectroscopy with those measured by mass spectrometry at 2542 points indicated good correlation between the two measurement methods.

PHARMACOLOGY

H.pylori exhibits high urease activity. The urea labeled with ^{13}C as a tracer in **UBIT tablet 100mg** is degraded to $^{13}CO_2$ and NH_3 by the urease activity of gastric *H. pylori* after ingestion, and the $^{13}CO_2$ that is formed is taken up by the blood and expired in the breath. Based on the above principle, the ^{13}C-urea breath test is a method of diagnosing *H. pylori* infection by detecting the $^{13}CO_2$ in the expired breath and determining the $\Delta\,^{13}CO_2$ after administration of urea (^{13}C).

PHYSICOCHEMISTRY

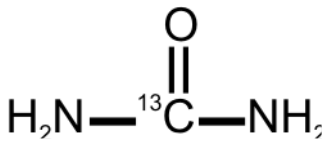
Nonproprietary name

Urea (^{13}C) (JAN)

Chemical name

^{13}C-urea

Structural formula:



Molecular formula

$^{13}CH_4N_2O$

Molecular weight

61.05

Description

Urea (^{13}C) occurs as colorless to white crystals or a crystalline powder and is odorless. It is highly soluble in water, soluble in ethanol (95), slightly soluble in acetonitrile, and practically insoluble in diethyl ether.

Melting point

133.5 - 135.5°C

PACKAGING

UBIT tablet 100mg: Box of 5 strips @ 2 tablets

STORAGE:

Store below 30°C
Use immediately after opening SP package*
*SP package = strips

CAUTION

Use only under direction of a physician or other qualified healthcare professional.

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