ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Helicobacter Test INFAI 75 mg powder for oral solution

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One jar contains 75 mg of ^{13}C-urea powder.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

White, crystalline powder for oral solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Helicobacter Test INFAI may be used for *in vivo* diagnosis of gastroduodenal *Helicobacter pylori* infection in:
- adults,
- adolescents, who are likely to have peptic ulcer disease.

This medicinal product is for diagnostic use only.

4.2 Posology and method of administration

This medicinal product should be administered by a healthcare professional and under appropriate medical supervision.

Posology

Helicobacter Test INFAI is a breath test for single administration. Patients from the age of 12 must take the contents of 1 jar with 75 mg.

Method of administration

For performance of the test, 200 ml 100 % orange juice or 1 g citric acid in 200 ml water for patients from the age of 12 and older (as a pre-administered test meal), as well as tap water (for dissolving the ^{13}C-urea powder) are necessary.

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.

4.3 Contraindications

The test must not be used in patients with documented or suspected gastric infection or atrophic gastritis, which might interfere with the urea breath test (see section 4.2).

4.4 Special warnings and precautions for use

A positive test alone does not constitute indication for eradication therapy. Differential diagnosis with invasive endoscopic methods might be indicated in order to examine the presence of any other complicating conditions, e.g. ulcer, autoimmune gastritis and malignancies.

There is insufficient data on the diagnostic liability of the Helicobacter Test INFAI to recommend its use in patients with gastrectomy.

For children from the age of 3, Helicobacter Test INFAI for children aged 3 to 11 is available.

In individual cases of A-gastritis (atrophic gastritis) the breath test may have false positive results; other tests may be required to confirm the *Helicobacter pylori* status.

If the patient vomits during the test procedure, necessitating the repetition of the test, this should be done in fasted condition and not before the following day (see section 4.2).

4.5 Interaction with other medicinal products and other forms of interaction

Helicobacter Test INFAI will be affected by all treatments interfering with *Helicobacter pylori* status or urease activity.

4.6 Fertility, pregnancy and lactation

It is not expected that the test procedure may be harmful during pregnancy or lactation.
It is recommended to take notice of the product information of eradication therapy products for their use during pregnancy and lactation.

4.7 Effects on ability to drive and use machines

Helicobacter Test INFAI has no influence on the ability to drive and use machines.

4.8 Undesirable effects

None known.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

Due to the fact that only 75 mg of ^{13}C-urea is delivered, an overdose is not expected.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other diagnostic agents, ATC code: VO4CX

For the amount of 75 mg ^{13}C-urea, which is administered per unit in the course of the breath test, no pharmacodynamic activity is described.

After oral ingestion the labelled urea reaches the gastric mucosa. In the presence of *Helicobacter pylori* the ^{13}C-urea is metabolised by the enzyme urease of *Helicobacter pylori*.

$$2H_2N(^{13}CO)NH_2 + 2H_2O \xrightarrow{\text{Enzyme urease}} 4NH_3 + 2\,^{13}CO_2$$

The carbon dioxide diffuses into the blood vessels. From there it is transported as bicarbonate into the lung and liberated as $^{13}CO_2$ with the exhaled air.

In the presence of bacterial urease the ratio of the $^{13}C/^{12}C$-carbon isotopes is significantly changed. The portion of $^{13}CO_2$ in the breath samples is determined by isotope-ratio-mass-spectrometry (IRMS) and stated as an absolute difference (Δδ-value) between the 00-minute- and the 30-minute-values.

Urease is produced in the stomach only by *Helicobacter pylori*. Other urease producing bacteria were seldom found in the gastric flora.

The cut off point for discriminating *Helicobacter pylori*-negative and positive patients is determined to be Δδ-value of 4 ‰, which means that an increase of the Δδ-value by more than 4 ‰ indicates an infection. In comparison to bioptic diagnostics of an infection with *Helicobacter pylori*, the breath test achieved in clinical trials on 457 patients, a sensitivity in the range of 96.5 % to 97.9 % [95 %-CI: 94.05 %-99.72 %], and a specificity range from 96.7 % to 100 %. [95 %-CI: 94.17 %-103.63 %], whereas in clinical trials on 93 adolescents from the age 12–17, a sensitivity of 97.7 % [90 %-CI: 91.3 %], and a specificity of 96.0 % [90 %-CI: 89.7 %] were achieved.

In the absence of bacterial urease, the whole amount of the administered urea after absorption from the gastrointestinal tract will be metabolised like the endogenous urea. Ammonia which is produced as described above by the bacterial hydrolysis is included into the metabolism as NH_4^+.

5.2 Pharmacokinetic properties

The orally applied ^{13}C-urea is metabolised to carbon dioxide and ammonia or is integrated into the body's own urea cycle. Any increase in $^{13}CO_2$ will be measured by isotopic analysis.

Absorption and distribution of $^{13}CO_2$ is faster than the urease reaction. Therefore, the rate-limiting step in the whole process is the cleavage of ^{13}C-urea by Helicobacter's urease.

Only in *Helicobacter pylori*-positive patients does the administration of 75 mg labelled urea lead to a significant increase of $^{13}CO_2$ in the breath sample within the first 30 minutes.

5.3 Preclinical safety data

No concerns in relation to the clinical use of the product.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

None.

6.2 Incompatibilities

Not applicable.

6.3 Shelf-life

3 years

6.4 Special precautions for storage

Do not store above 25 °C.

6.5 Nature and contents of container

A test set contains the following parts:

No.	Component	Quantity
1	Jar (10 ml volume, polystyrene with polyethylene snap cap) containing 75 mg ^{13}C-urea powder for oral solution	1
2	Labelled sample glass- or plastic- containers for sampling, storing and transporting the breath samples for analysis: Sampling time: 00-minute-value Sampling time: 30-minute-value	 2 2
3	Bendable straw for collection of the breath samples into the corresponding sample containers	1
4	Data sheet for patient documentation	1
5	Package leaflet	1
6	Page of barcode labels and sticker	1

6.6 Special precautions for disposal and other handling

1. The test is to be performed in the presence of a qualified person.
2. Each patient should be documented according to the provided data sheet. It is recommended to perform the test with the patient being in a resting position.
3. The test starts with the collection of samples for the determination of baseline-value (00-minute-value):
   - Take the straw and the two sample tubes with the label "Sampling time: 00-minute-value" out of the test set.
   - Remove the stopper from one of the sample tubes, unwrap the straw and place the straw into the container.
   - Now the patient breathes gently through the straw until the inner surface of the sample tube steams up.
   - By continuously breathing the patient must pull out the straw and immediately close the sample tube with its stopper.
     (If the sample tube remains open for more than 30 seconds, the test result might be falsified.)
   - Hold the sample tube upright and stick the bar-code label marked "00-minute-value" round the sample tube, so that the lines of the bar-code are horizontal.
4. Fill up the second sample tube (Label "Sampling time: 00-minute-value") with breath by following the same procedure.
5. Now 200 ml of 100 % orange juice or 1 g citric acid in 200 ml water must be drunk by the patient without delay.
6. Now the preparation of the test solution follows:
   - The jar labelled "^{13}C-urea powder" is taken from the test set, opened, and filled up to three quarters of its volume with tap water.
   - Close the jar and shake it carefully until all the powder is dissolved. Pour the contents into a drinking glass.
   - Fill the ^{13}C-urea jar to the brim with water for a second and third time and add these contents to the drinking glass (total volume of tap water should be approximately 30 ml).

7. This test solution must now be drunk immediately by the patient, and the time of application must be noted.
8. Thirty minutes after administration of the test solution (point 7), collect the 30-minute-value samples in the two containers which are left in the test package (Label “Sampling time: 30-minute-value”), as described under steps 3 to 4. Use the bar-code labels marked “30-minute-value” for these samples.
9. Put the relevant bar-code label on the data sheet for patient documentation. Finally seal the package with the sticker.
10. The sample tubes have to be sent in the original packaging, for analysis, to a qualified laboratory.

Analysis of breath samples and testing specification for laboratories

The breath samples, collected in 10 ml glass- or plastic sample tubes, are analysed by isotope ratio mass spectrometry (IRMS).

The analysis of the $^{13}C/^{12}C$-ratio in carbon dioxide of breath is an integrated part of the diagnostic test Helicobacter Test INFAI. The accuracy of the test strongly depends on the quality of the breath analysis. The specification of breath analysis parameters like linearity, stability (reference gas precision), and precision of measurement are fundamental for the accuracy of the system.

It has to be ensured that the analysis is carried out by a qualified laboratory. The method validated in the application is as follows:

- Sample preparation for (IRMS)

To determine the $^{13}C/^{12}C$-ratio of carbon dioxide in breath by mass spectrometric analysis the carbon dioxide must be separated from the breath and introduced into the mass spectrometer. The automatic preparation system for isotope mass spectrometers which is dedicated for breath test analysis is based on a gas-chromatographic continuous flow separation technique.

Water is removed from the sample by means of a Nafion water trap or the gas-chromatographic preparation system that separates the individual gases in a gas chromatographic column with Helium as eluent. Passing the column the separated gas species of breath are detected by an ionisation detector. The fraction of carbon dioxide gas, identified by its characteristic retention time, is introduced into mass spectrometer.

- Mass spectrometric analysis

To analyse the separated carbon dioxide sample gas its molecules must be ionised, formed into a beam, accelerated by an electric field, deflected in a magnetic field, and finally detected. These five processes take place in the analyser of a mass spectrometer, which consists of three separate sections: the source, flight tube, and collector. Ionisation, beam formation and acceleration all occur in the source, magnetic deflection takes place in the flight tube and detection takes place in the collector.

- Sample inlet

For introduction of the carbon dioxide into the analyser many sample inlet systems are available. For breath test analysis the individual balancing of the carbon dioxide of the sample to a reference standard gas is essential. This ensures the high accuracy of this system, as calculation of the isotopic content in carbon dioxide is done with respect to an independent standard.

- Specifications for determining $^{13}C/^{12}C$-ratios

The breath test concept relies on the administration of a specifically ^{13}C-labelled urea whose metabolite utilisation is monitored by measuring $^{13}CO_2$ in the expired breath gas.

- The mass spectrometer must be capable of:

Multiple replicate analyses:	Minimum of 3 replicate analyses of the same sample during operation
Security access:	Storing of operating parameters and of results under security access to avoid later manipulation
Adjustment:	$^{13}C/^{12}C$-ratio with respect to Pee Dee Beliminate (PDB)
Sample loop:	< 200 µl

The principal tests to verify the specifications are linearity, stability (reference gas precision), and precision of measurement.

- All mass spectrometers for breath analysis must comply with the following specifications:

Linearity:	≤ 0.5 ‰ for breath samples varying between 1 % and 7 % CO_2-concentration
Stability:	≤ 0.2 ‰ on 10 consecutive pulses
Precision of measurement:	≤ 0.3 ‰ for ^{13}C at natural abundance using a 10 ml breath sample tube with 3 % CO_2 breath concentration

Helicobacter pylori infection is present if the difference in $^{13}C/^{12}C$ of baseline-value and 30-minute-value exceeds 4.0 ‰.

Alternatively, any other suitable-validated method may be used, carried out by any objectively qualified laboratory.

7. MARKETING AUTHORISATION HOLDER

INFAI GmbH
Riehler Str. 36
D-50668 Köln
Germany

8. MARKETING AUTHORISATION NUMBER

EU/1/97/045/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 14 August 1997
Date of latest renewal: 14 August 2007

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

1. NAME OF THE MEDICINAL PRODUCT

Helicobacter Test INFAI 75 mg powder for oral solution

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One jar contains 75 mg of ^{13}C-urea powder.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

White, crystalline powder for oral solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Helicobacter Test INFAI may be used for *in vivo* diagnosis of gastroduodenal *Helicobacter pylori* infection in:
- adults,
- adolescents, who are likely to have peptic ulcer disease.

This medicinal product is for diagnostic use only.

4.2 Posology and method of administration

This medicinal product should be administered by a healthcare professional and under appropriate medical supervision.

Posology

Helicobacter Test INFAI is a breath test for single administration. Patients from the age of 12 must take the contents of 1 jar with 75 mg.

Method of administration

For performance of the test, 200 ml 100 % orange juice or 1 g citric acid in 200 ml water for patients from the age of 12 and older (as a pre-administered test meal), as well as tap water (for dissolving the ^{13}C-urea powder) are necessary.

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.

4.3 Contraindications

The test must not be used in patients with documented or suspected gastric infection or atrophic gastritis, which might interfere with the urea breath test (see section 4.2).

4.4 Special warnings and precautions for use

A positive test alone does not constitute indication for eradication therapy. Differential diagnosis with invasive endoscopic methods might be indicated in order to examine the presence of any other complicating conditions, e.g. ulcer, autoimmune gastritis and malignancies.

There is insufficient data on the diagnostic liability of the Helicobacter Test INFAI to recommend its use in patients with gastrectomy.

For children from the age of 3, Helicobacter Test INFAI for children aged 3 to 11 is available.

In individual cases of A-gastritis (atrophic gastritis) the breath test may have false positive results; other tests may be required to confirm the *Helicobacter pylori* status.

If the patient vomits during the test procedure, necessitating the repetition of the test, this should be done in fasted condition and not before the following day (see section 4.2).

4.5 Interaction with other medicinal products and other forms of interaction

Helicobacter Test INFAI will be affected by all treatments interfering with *Helicobacter pylori* status or urease activity.

4.6 Fertility, pregnancy and lactation

It is not expected that the test procedure may be harmful during pregnancy or lactation.
It is recommended to take notice of the product information of eradication therapy products for their use during pregnancy and lactation.

4.7 Effects on ability to drive and use machines

Helicobacter Test INFAI has no influence on the ability to drive and use machines.

4.8 Undesirable effects

None known.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

Due to the fact that only 75 mg of ^{13}C-urea is delivered, an overdose is not expected.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other diagnostic agents, ATC code: VO4CX

For the amount of 75 mg ^{13}C-urea, which is administered per unit in the course of the breath test, no pharmacodynamic activity is described.

After oral ingestion the labelled urea reaches the gastric mucosa. In the presence of *Helicobacter pylori* the ^{13}C-urea is metabolised by the enzyme urease of *Helicobacter pylori*.

$$2H_2N(^{13}CO)NH_2 + 2H_2O \xrightarrow{\text{Enzyme urease}} 4NH_3 + 2^{13}CO_2$$

The carbon dioxide diffuses into the blood vessels. From there it is transported as bicarbonate into the lung and liberated as $^{13}CO_2$ with the exhaled air.

In the presence of bacterial urease the ratio of the $^{13}C/^{12}C$-carbon isotopes is significantly changed. The portion of $^{13}CO_2$ in the breath samples is determined by non-dispersive infrared spectrometry and stated as an absolute difference (Δδ-value) between the 00-minute- and the 30-minute-values.

Urease is produced in the stomach only by *Helicobacter pylori*. Other urease producing bacteria were seldom found in the gastric flora.

The cut off point for discriminating *Helicobacter pylori*-negative and positive patients is determined to be Δδ-value of 4 ‰, which means that an increase of the Δδ-value by more than 4 ‰ indicates an infection. In comparison to bioptic diagnostics of an infection with *Helicobacter pylori*, the breath test achieved in clinical trials on 457 patients, a sensitivity in the range of 96.5 % to 97.9 % [95 %-CI: 94.05 %-99.72 %], and a specificity range from 96.7 % to 100 %. [95 %-CI: 94.17 %-103.63 %].

In the absence of bacterial urease, the whole amount of the administered urea after absorption from the gastrointestinal tract will be metabolised like the endogenous urea. Ammonia which is produced as described above by the bacterial hydrolysis is included into the metabolism as NH_4^+.

5.2 Pharmacokinetic properties

The orally applied ^{13}C-urea is metabolised to carbon dioxide and ammonia or is integrated into the body's own urea cycle. Any increase in $^{13}CO_2$ will be measured by isotopic analysis.

Absorption and distribution of $^{13}CO_2$ is faster than the urease reaction. Therefore, the rate-limiting step in the whole process is the cleavage of ^{13}C-urea by Helicobacter's urease.

Only in *Helicobacter pylori*-positive patients does the administration of 75 mg labelled urea lead to a significant increase of $^{13}CO_2$ in the breath sample within the first 30 minutes.

5.3 Preclinical safety data

No concerns in relation to the clinical use of the product.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

None.

6.2 Incompatibilities

Not applicable.

6.3 Shelf-life

3 years

6.4 Special precautions for storage

Do not store above 25 °C.

6.5 Nature and contents of container

A test set contains 1 jar with the additional components:

No.	Component	Quantity
1	Jar (10 ml volume, polystyrene with polyethylene snap cap) containing 75 mg ^{13}C-urea powder for oral solution	1
2	Breath bags: Sampling time: 00-minute-value Sampling time: 30-minute-value	 1 1
3	Bendable straw for collection of the breath samples into the corresponding breath bags	1
4	Data sheet for patient documentation	1
5	Package leaflet	1
6	Page of barcode labels and sticker	1

A test set contains 50 jars with the additional components:

No.	Component	Quantity
1	Jar (10 ml volume, polystyrene with polyethylene snap cap) containing 75 mg ^{13}C-urea powder for oral solution	50
2	Breath bags: Sampling time: 00-minute-value Sampling time: 30-minute-value	 50 50
3	Bendable straw for collection of the breath samples into the corresponding breath bags	50
4	Data sheet for patient documentation	50
5	Package leaflet	50
6	Page of barcode labels and sticker	50

6.6 Special precautions for disposal and other handling

1. The test is to be performed in the presence of a qualified person.
2. Each patient should be documented according to the provided data sheet. It is recommended to perform the test with the patient being in a resting position.
3. The test starts with the collection of samples for the determination of baseline-value (00-minute-value):
   - Take the straw and the breath bag with the label "Sampling time: 00-minute-value" out of the test set.
   - Remove the stopper from the breath bag, unwrap the straw and place the straw into the breath bag.
   - Now the patient breathes gently through the straw.
   - By continuously breathing the patient must pull out the straw and immediately close the breath bag with its stopper.
     (If the breath bag remains open for more than 30 seconds, the test result might be falsified.)
   - Hold the breath bag upright and stick the bar-code label marked "00-minute-value" on the breath bag.

4. Now 200 ml of 100 % orange juice or 1 g citric acid in 200 ml water must be drunk by the patient without delay.
5. Now the preparation of the test solution follows:
   - The jar labelled "^{13}C-urea powder" is taken from the test set, opened, and filled up to three quarters of its volume with tap water.
   - Close the jar and shake it carefully until all the powder is dissolved. Pour the contents into a drinking glass.
   - Fill the ^{13}C-urea jar to the brim with water for a second and third time and add these contents to the drinking glass (total volume of tap water should be approximately 30 ml).
6. This test solution must now be drunk immediately by the patient, and the time of application must be noted.
7. Thirty minutes after administration of the test solution (point 6), collect the 30-minute-value sample in the breath bag, which is left in the test package (Label "Sampling time: 30-minute-value"), as described under step 3. Use the bar-code label marked "30-minute-value" for this sample.
8. Put the relevant bar-code label on the data sheet for patient documentation. Finally seal the package with the sticker.
9. The breath bags have to be sent in the original packaging, for analysis, to a qualified laboratory.

Analysis of breath samples and testing specification for laboratories

The breath samples, collected in 100 ml breath bags, are analysed by non-dispersive infrared spectrometry (NDIR).

The analysis of the ^{13}C/^{12}C-ratio in carbon dioxide of breath is an integrated part of the diagnostic test Helicobacter Test INFAI. The accuracy of the test strongly depends on the quality of the breath analysis. The specification of breath analysis parameters like linearity, stability (reference gas precision), and precision of measurement are fundamental for the accuracy of the system.

It has to be ensured that the analysis is carried out by a qualified laboratory. It is recommended to measure as soon as possible after the breath collection, in any case not later than 4 weeks.

The method validated in the application is as follows:

- Sample preparation for Infrared Spectroscopy (NDIR)

The determination of ^{13}C/^{12}C-ratio in the carbon dioxide of the breath samples is carried out directly in the breath. The breath from the bags will be introduced into the NDIR spectrometer using a variable gas pump. The water content of the breath sample will be kept mostly constant through Nafion water trap. For calibration and measurement necessary CO_2-free air (zero-gas) will be produced via an integrated CO_2-absorber in the analysator.

- Infrared spectroscopic analysis

To analyse the carbon dioxide in breath a broad band infrared radiation bunch emitted by an infrared radiation source is alternately sent through the measuring chamber and a reference chamber by means of a beam chopper. The modulated infrared beams then enter the infrared detectors, which are double layer transmission detectors with a front, and a rear chamber each filled with one of the isotopicly pure gases ($^{13}CO_2$ or $^{12}CO_2$, respectively) to be measured. The infrared radiation in the measuring chamber is weakened by the gas component to be measured. Thus the radiation equilibrium between measuring and comparative beam is disturbed. In consequence there is a temperature fluctuation, which in its turn causes a fluctuating pressure in the front chamber of the infrared detector. A membrane capacitor connected with this chamber, which is exposed to a high resistance direct voltage, transforms these pressure fluctuations into an alternating voltage, which is a measure of the isotopic composition of breath carbon dioxide.

- Sample Inlet

A semi-automatic sample inlet system injects the measuring gas in definite amounts into the zero gas circulating in the gas circuit of the infrared spectrometer. This enables measurement of the $^{13}C/^{12}C$-ratio at any CO_2 concentration above 1 %.

- Specifications for determining $^{13}C/^{12}C$-ratios

The breath test concept is based upon the oral administration of ^{13}C-labelled urea whose enzymatic hydrolysis is monitored by measuring $^{13}CO_2$ in breath using non-dispersive infrared spectrometry.

- Infrared spectrometers for breath analysis must comply with the following specifications:

Multiple replicate analyses:	Minimum of 3 replicate analyses of the same sample during operation
Security access:	Storing of operating parameters and of results under security access to avoid later manipulation

For verifying the specifications linearity, stability, and precision of measurement have to be tested.

Zero point adjustment of the detectors by means of the zero gas generated in the spectrometer. End-point adjustment of the detectors by means of calibration gases of precisely known concentration.

Linearity:	≤ 0.5 ‰ for breath samples varying between 1 % and 7 % CO_2-concentration
Stability:	≤ 0.3 ‰ at 10 consecutive pulses
Precision of measurement:	≤ 0.5 ‰ for ^{13}C at natural abundance using a 100 ml breath bag with 3 % CO_2 breath concentration

Helicobacter pylori infection is present if the difference in $^{13}C/^{12}C$ of baseline-value and 30-minute-value exceeds 4.0 ‰**.**

Alternatively, any other suitable-validated method may be used, carried out by any objectively qualified laboratory.

7. MARKETING AUTHORISATION HOLDER

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D-50668 Köln
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8. MARKETING AUTHORISATION NUMBERS

EU/1/97/045/002
EU/1/97/045/004

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 14 August 1997
Date of latest renewal: 14 August 2007

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

1. NAME OF THE MEDICINAL PRODUCT

Helicobacter Test INFAI for children of the age 3-11 45 mg powder for oral solution

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One jar contains 45 mg of ^{13}C-urea powder.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

White, crystalline powder for oral solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Helicobacter Test INFAI for children of the age 3-11 may be used for *in vivo* diagnosis of gastroduodenal *Helicobacter pylori* infection:
- for the evalutation of the success of eradication treatment, or,
- when invasive tests cannot be performed, or
- when there are discordant results arising from invasive tests.

This medicinal product is for diagnostic use only.

4.2 Posology and method of administration

This medicinal product should be administered by a healthcare professional and under appropriate medical supervision.

Posology

Helicobacter Test INFAI for children of the age 3-11 is a breath test for single administration. Children from the age of 3 to 11 must take the contents of 1 jar with 45 mg.

Method of administration

For performance of the test, 100 ml 100 % orange juice for patients from the age of 3 to 11 (as a pre-administered test meal), as well as tap water (for dissolving the ^{13}C-urea powder) are necessary.

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.

4.3 Contraindications

The test must not be used in patients with documented or suspected gastric infection or atrophic gastritis, which might interfere with the urea breath test (see section 4.2).

4.4 Special warnings and precautions for use

A positive test alone does not constitute indication for eradication therapy. Differential diagnosis with invasive endoscopic methods might be indicated in order to examine the presence of any other complicating conditions, e.g. ulcer, autoimmune gastritis and malignancies.

There is insufficient data on the diagnostic liability of the Helicobacter Test INFAI for children of the age 3-11 to recommend its use in patients with gastrectomy and in patients younger than 3 years of age.

In individual cases of A-gastritis (atrophic gastritis) the breath test may have false positive results; other tests may be required to confirm the *Helicobacter pylori* status.

If the patient vomits during the test procedure, necessitating the repetition of the test, this should be done in fasted condition and not before the following day (see section 4.2).

4.5 Interaction with other medicinal products and other forms of interaction

Helicobacter Test INFAI for children of the age 3-11 will be affected by all treatments interfering with *Helicobacter pylori* status or urease activity.

4.6 Fertility, pregnancy and lactation

Not applicable.

4.7 Effects on ability to drive and use machines

None.

4.8 Undesirable effects

None known.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

Due to the fact that only 45 mg of ^{13}C-urea is delivered, an overdose is not expected.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other diagnostic agents, ATC code: VO4CX

For the amount of 45 mg ^{13}C-urea, which is administered per unit in the course of the breath test, no pharmacodynamic activity is described.

After oral ingestion the labelled urea reaches the gastric mucosa. In the presence of *Helicobacter pylori* the ^{13}C-urea is metabolised by the enzyme urease of *Helicobacter pylori*.

$$2H_2N(^{13}CO)NH_2 + 2H_2O \xrightarrow{\text{Enzyme urease}} 4NH_3 + 2^{13}CO_2$$

The carbon dioxide diffuses into the blood vessels. From there it is transported as bicarbonate into the lung and liberated as $^{13}CO_2$ with the exhaled air.

In the presence of bacterial urease the ratio of the $^{13}C/^{12}C$-carbon isotopes is significantly changed. The portion of $^{13}CO_2$ in the breath samples is determined by isotope-ratio-mass-spectrometry (IRMS) and stated as an absolute difference (Δδ-value) between the 00-minute- and the 30-minute-values.

Urease is produced in the stomach only by *Helicobacter pylori*. Other urease producing bacteria were seldom found in the gastric flora.

The cut off point for discriminating *Helicobacter pylori*-negative and positive patients is determined to be Δδ-value of 4 ‰, which means that an increase of the Δδ-value by more than 4 ‰ indicates an infection. In comparison to bioptic diagnostics of an infection with *Helicobacter pylori*, the breath test achieved in a clinical trial on 168 patients from the age of 3 to 11, a sensitivity of 98.4 % [90 %-CI: ≥ 93.9 %], and a specificity of 98.1 % [90 %-CI: ≥ 95.1 %].

In the absence of bacterial urease, the whole amount of the administered urea after absorption from the gastrointestinal tract will be metabolised like the endogenous urea. Ammonia which is produced as described above by the bacterial hydrolysis is included into the metabolism as NH_4^+.

5.2 Pharmacokinetic properties

The orally applied ^{13}C-urea is metabolised to carbon dioxide and ammonia or is integrated into the body's own urea cycle. Any increase in $^{13}CO_2$ will be measured by isotopic analysis.

Absorption and distribution of $^{13}CO_2$ is faster than the urease reaction. Therefore, the rate-limiting step in the whole process is the cleavage of ^{13}C-urea by Helicobacter's urease.

Only in *Helicobacter pylori*- positive patients does the administration of 45 mg labelled urea lead to a significant increase of $^{13}CO_2$ in the breath sample within the first 30 minutes.

5.3 Preclinical safety data

No concerns in relation to the clinical use of the product.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

None.

6.2 Incompatibilities

Not applicable.

6.3 Shelf-life

3 years

6.4 Special precautions for storage

Do not store above 25 °C.

6.5 Nature and contents of container

A test set contains the following parts:

No.	Component	Quantity
1	Jar (10 ml volume, polystyrene with polyethylene snap cap) containing 45 mg ^{13}C-urea powder for oral solution	1
2	Labelled sample glass- or plastic- containers for sampling, storing and transporting the breath samples for analysis: Sampling time: 00-minute-value Sampling time: 30-minute-value	 2 2
3	Bendable straw for collection of the breath samples into the corresponding sample containers	1
4	Data sheet for patient documentation	1
5	Package leaflet	1
6	Page of barcode labels and sticker	1

6.6 Special precautions for disposal and other handling

1. The test is to be performed in the presence of a qualified person.
2. Each patient should be documented according to the provided data sheet. It is recommended to perform the test with the patient being in a resting position.
3. The test starts with the collection of samples for the determination of baseline-value (00-minute-value):
   - Take the straw and the two sample tubes with the label "Sampling time: 00-minute-value" out of the test set.
   - Remove the stopper from one of the sample tubes, unwrap the straw and place the straw into the container.
   - Now the patient breathes gently through the straw until the inner surface of the sample tube steams up.
   - By continuously breathing the patient must pull out the straw and immediately close the sample tube with its stopper.
     (If the sample tube remains open for more than 30 seconds, the test result might be falsified.)
   - Hold the sample tube upright and stick the bar-code label marked "00-minute-value" round the sample tube, so that the lines of the bar-code are horizontal.
4. Fill up the second sample tube (Label "Sampling time: 00-minute-value") with breath by following the same procedure.
5. Now 100 ml of 100 % orange juice must be drunk by the patient without delay.
6. Now the preparation of the test solution follows:
   - The jar labelled "^{13}C-urea powder" is taken from the test set, opened, and filled up to three quarters of its volume with tap water.
   - Close the jar and shake it carefully until all the powder is dissolved. Pour the contents into a drinking glass.
   - Fill the ^{13}C-urea jar to the brim with water for a second and third time and add these contents to the drinking glass (total volume of tap water should be approximately 30 ml).
7. This test solution must now be drunk immediately by the patient, and the time of application must be noted.
8. Thirty minutes after administration of the test solution (point 7), collect the 30-minute-value samples in the two containers which are left in the test package (Label "Sampling time: 30-minute-value"), as described under steps 3 to 4. Use the bar-code labels marked "30-minute-value" for these samples.

9. Put the relevant bar-code label on the data sheet for patient documentation. Finally seal the package with the sticker.
10. The sample tubes have to be sent in the original packaging, for analysis, to a qualified laboratory.

Analysis of breath samples and testing specification for laboratories

The breath samples, collected in 10 ml glass- or plastic sample tubes, are analysed by isotope ratio mass spectrometry (IRMS).

The analysis of the $^{13}C/^{12}C$-ratio in carbon dioxide of breath is an integrated part of the diagnostic test Helicobacter Test INFAI. The accuracy of the test strongly depends on the quality of the breath analysis. The specification of breath analysis parameters like linearity, stability (reference gas precision), and precision of measurement are fundamental for the accuracy of the system.

It has to be ensured that the analysis is carried out by a qualified laboratory. The method validated in the application is as follows:

- Sample preparation for (IRMS)

To determine the $^{13}C/^{12}C$-ratio of carbon dioxide in breath by mass spectrometric analysis the carbon dioxide must be separated from the breath and introduced into the mass spectrometer. The automatic preparation system for isotope mass spectrometers which is dedicated for breath test analysis is based on a gas-chromatographic continuous flow separation technique.

Water is removed from the sample by means of a Nafion water trap or the gas-chromatographic preparation system that separates the individual gases in a gas chromatographic column with Helium as eluent. Passing the column the separated gas species of breath are detected by an ionisation detector. The fraction of carbon dioxide gas, identified by its characteristic retention time, is introduced into mass spectrometer.

- Mass spectrometric analysis

To analyse the separated carbon dioxide sample gas its molecules must be ionised, formed into a beam, accelerated by an electric field, deflected in a magnetic field, and finally detected. These five processes take place in the analyser of a mass spectrometer, which consists of three separate sections: the source, flight tube, and collector. Ionisation, beam formation and acceleration all occur in the source, magnetic deflection takes place in the flight tube and detection takes place in the collector.

- Sample inlet

For introduction of the carbon dioxide into the analyser many sample inlet systems are available. For breath test analysis the individual balancing of the carbon dioxide of the sample to a reference standard gas is essential. This ensures the high accuracy of this system, as calculation of the isotopic content in carbon dioxide is done with respect to an independent standard.

- Specifications for determining $^{13}C/^{12}C$-ratios

The breath test concept relies on the administration of a specifically ^{13}C-labelled urea whose metabolite utilisation is monitored by measuring $^{13}CO_2$ in the expired breath gas.

- The mass spectrometer must be capable of:

Multiple replicate analyses: Minimum of 3 replicate analyses of the same sample during operation

Security access:	Storing of operating parameters and of results under security access to avoid later manipulation
Adjustment:	$^{13}C/^{12}C$-ratio with respect to Pee Dee Beliminate (PDB)
Sample loop:	< 200 µl

The principal tests to verify the specifications are linearity, stability (reference gas precision), and precision of measurement.

- All mass spectrometers for breath analysis must comply with the following specifications:

Linearity:	≤ 0.5 ‰ for breath samples varying between 1 % and 7 % CO_2-concentration
Stability:	≤ 0.2 ‰ on 10 consecutive pulses
Precision of measurement:	≤ 0.3 ‰ for ^{13}C at natural abundance using a 10 ml breath sample tube with 3 % CO_2 breath concentration

Helicobacter pylori infection is present if the difference in $^{13}C/^{12}C$ of baseline-value and 30-minute-value exceeds 4.0 ‰.

Alternatively, any other suitable-validated method may be used, carried out by any objectively qualified laboratory.

7. MARKETING AUTHORISATION HOLDER

INFAI GmbH
Riehler Str. 36
D-50668 Köln
Germany

8. MARKETING AUTHORISATION NUMBER

EU/1/97/045/003

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 14 August 1997
Date of latest renewal: 14 August 2007

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

1. NAME OF THE MEDICINAL PRODUCT

Helicobacter Test INFAI 75 mg powder for oral solution

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One jar contains 75 mg of ^{13}C-urea powder.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

White, crystalline powder for oral solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Helicobacter Test INFAI may be used for *in vivo* diagnosis of gastroduodenal *Helicobacter pylori* infection in:
- adults,
- adolescents, who are likely to have peptic ulcer disease.

This medicinal product is for diagnostic use only.

4.2 Posology and method of administration

This medicinal product should be administered by a healthcare professional and under appropriate medical supervision.

Posology

Helicobacter Test INFAI is a breath test for single administration. Patients from the age of 12 must take the contents of 1 jar with 75 mg.

Method of administration

For performance of the test, 200 ml 100 % orange juice or 1 g citric acid in 200 ml water for patients from the age of 12 and older (as a pre-administered test meal), as well as tap water (for dissolving the ^{13}C-urea powder) are necessary.

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.

4.3 Contraindications

The test must not be used in patients with documented or suspected gastric infection or atrophic gastritis, which might interfere with the urea breath test (see section 4.2).

4.4 Special warnings and precautions for use

A positive test alone does not constitute indication for eradication therapy. Differential diagnosis with invasive endoscopic methods might be indicated in order to examine the presence of any other complicating conditions, e.g. ulcer, autoimmune gastritis and malignancies.

There is insufficient data on the diagnostic liability of the Helicobacter Test INFAI to recommend its use in patients with gastrectomy.

For children from the age of 3, Helicobacter Test INFAI for children aged 3 to 11 is available.

In individual cases of A-gastritis (atrophic gastritis) the breath test may have false positive results; other tests may be required to confirm the *Helicobacter pylori* status.

If the patient vomits during the test procedure, necessitating the repetition of the test, this should be done in fasted condition and not before the following day (see section 4.2).

4.5 Interaction with other medicinal products and other forms of interaction

Helicobacter Test INFAI will be affected by all treatments interfering with *Helicobacter pylori* status or urease activity.

4.6 Fertility, pregnancy and lactation

It is not expected that the test procedure may be harmful during pregnancy or lactation.
It is recommended to take notice of the product information of eradication therapy products for their use during pregnancy and lactation.

4.7 Effects on ability to drive and use machines

Helicobacter Test INFAI has no influence on the ability to drive and use machines.

4.8 Undesirable effects

None known.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

Due to the fact that only 75 mg of ^{13}C-urea is delivered, an overdose is not expected.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other diagnostic agents, ATC code: VO4CX

For the amount of 75 mg ^{13}C-urea, which is administered per unit in the course of the breath test, no pharmacodynamic activity is described.

After oral ingestion the labelled urea reaches the gastric mucosa. In the presence of *Helicobacter pylori* the ^{13}C-urea is metabolised by the enzyme urease of *Helicobacter pylori*.

$$2H_2N(^{13}CO)NH_2 + 2H_2O \xrightarrow{\text{Enzyme urease}} 4NH_3 + 2^{13}CO_2$$

The carbon dioxide diffuses into the blood vessels. From there it is transported as bicarbonate into the lung and liberated as $^{13}CO_2$ with the exhaled air.

In the presence of bacterial urease the ratio of the $^{13}C/^{12}C$-carbon isotopes is significantly changed. The portion of $^{13}CO_2$ in the breath samples is determined by non-dispersive infrared spectrometry and stated as an absolute difference (Δδ-value) between the 00-minute- and the 30-minute-values.

Urease is produced in the stomach only by *Helicobacter pylori*. Other urease producing bacteria were seldom found in the gastric flora.

The cut off point for discriminating *Helicobacter pylori*-negative and positive patients is determined to be Δδ-value of 4 ‰, which means that an increase of the Δδ-value by more than 4 ‰ indicates an infection. In comparison to bioptic diagnostics of an infection with *Helicobacter pylori*, the breath test achieved in clinical trials on 457 patients, a sensitivity in the range of 96.5 % to 97.9 % [95 %-CI: 94.05 %-99.72 %], and a specificity range from 96.7 % to 100 % [95 %-CI: 94.17 %-103.63 %].

In the absence of bacterial urease, the whole amount of the administered urea after absorption from the gastrointestinal tract will be metabolised like the endogenous urea. Ammonia which is produced as described above by the bacterial hydrolysis is included into the metabolism as NH_4^+.

5.2 Pharmacokinetic properties

The orally applied ^{13}C-urea is metabolised to carbon dioxide and ammonia or is integrated into the body's own urea cycle. Any increase in $^{13}CO_2$ will be measured by isotopic analysis.

Absorption and distribution of $^{13}CO_2$ is faster than the urease reaction. Therefore, the rate-limiting step in the whole process is the cleavage of ^{13}C-urea by Helicobacter's urease.

Only in *Helicobacter pylori*-positive patients does the administration of 75 mg labelled urea lead to a significant increase of $^{13}CO_2$ in the breath sample within the first 30 minutes.

5.3 Preclinical safety data

No concerns in relation to the clinical use of the product.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

None.

6.2 Incompatibilities

Not applicable.

6.3 Shelf-life

3 years

6.4 Special precautions for storage

Do not store above 25 °C.

6.5 Nature and contents of container

A test set contains 50 jars with the additional components:

No.	Component	Quantity
1	Jar (10 ml volume, polystyrene with polyethylene snap cap) containing 75 mg ^{13}C-urea powder for oral solution	50
2	Data sheet for patient documentation	50
3	Package leaflet	50
4	Page of barcode labels and sticker	50

6.6 Special precautions for disposal and other handling

1. The test is to be performed in the presence of a qualified person.
2. Each patient should be documented according to the provided data sheet. It is recommended to perform the test with the patient being in a resting position.
3. The test starts with the collection of samples for the determination of baseline-value (00-minute-value):
   - Take the straw and the breath sample containers (tubes or breath bag) with the label "Sampling time: 00-minute-value" out of the test set.
   - Remove the stopper from one of the breath sample containers (tube or breath bag), unwrap the straw and place the straw into the container.
   - Now the patient breathes gently through the straw into the breath sample container.
   - By continuously breathing the patient must pull out the straw and immediately close the breath sample container (tube or breath bag) with its stopper.
     (If the breath sample container remains open for more than 30 seconds, the test result might be falsified.)
   - Hold the sample tube or breath bag upright and stick the bar-code label marked "00-minute-value" on the container.
4. Fill up the second sample tube (Label "Sampling time: 00-minute-value") with breath by following the same procedure. For infrared analysis, only one breath bag is used.
5. Now 200 ml of 100 % orange juice or 1 g citric acid in 200 ml water must be drunk by the patient without delay.
6. Now the preparation of the test solution follows:
   - The jar labelled "^{13}C-urea powder" is taken from the test set, opened, and filled up to three quarters of its volume with tap water.
   - Close the jar and shake it carefully until all the powder is dissolved. Pour the contents into a drinking glass.
   - Fill the ^{13}C-urea jar to the brim with water for a second and third time and add these contents to the drinking glass (total volume of tap water should be approximately 30 ml).
7. This test solution must now be drunk immediately by the patient, and the time of application must be noted.
8. Thirty minutes after administration of the test solution (point 7), collect the 30-minute-value samples in the breath sample container (tube or breath bags) (Label "Sampling time: 30-minute-value"), as described under steps 3 to 4. Use the bar-code labels marked "30-minute-value" for these samples.
9. Put the relevant bar-code label on the data sheet for patient documentation. Finally seal the package with the sticker.

10. The breath sample containers (tube or breath bags) have to be sent for analysis, to a qualified laboratory.

Analysis of breath samples and testing specification for laboratories for infrared analyzer or mass spectrometry (IRMS)

Infrared spectroscopy (NDIR)

The breath samples, collected in 100 ml breath bags, are analysed by non-dispersive infrared spectrometry (NDIR).

The analysis of the $^{13}C/^{12}C$-ratio in carbon dioxide of breath is an integrated part of the diagnostic test Helicobacter Test INFAI. The accuracy of the test strongly depends on the quality of the breath analysis. The specification of breath analysis parameters like linearity, stability (reference gas precision), and precision of measurement are fundamental for the accuracy of the system.

It has to be ensured that the analysis is carried out by a qualified laboratory. It is recommended to measure as soon as possible after the breath collection, in any case not later than 4 weeks.

The method validated in the application is as follows:

- Sample preparation for Infrared Spectroscopy (NDIR)

The determination of $^{13}C/^{12}C$-ratio in the carbon dioxide of the breath samples is carried out directly in the breath. The breath from the bags will be introduced into the NDIR spectrometer using a variable gas pump. The water content of the breath sample will be kept mostly constant through Nafion water trap. For calibration and measurement necessary CO_2-free air (zero-gas) will be produced via an integrated CO_2-absorber in the analysator.

- Infrared spectroscopic analysis

To analyse the carbon dioxide in breath a broad band infrared radiation bunch emitted by an infrared radiation source is alternately sent through the measuring chamber and a reference chamber by means of a beam chopper. The modulated infrared beams then enter the infrared detectors, which are double layer transmission detectors with a front, and a rear chamber each filled with one of the isotopicly pure gases ($^{13}CO_2$ or $^{12}CO_2$, respectively) to be measured. The infrared radiation in the measuring chamber is weakened by the gas component to be measured. Thus the radiation equilibrium between measuring and comparative beam is disturbed. In consequence there is a temperature fluctuation, which in its turn causes a fluctuating pressure in the front chamber of the infrared detector. A membrane capacitor connected with this chamber, which is exposed to a high resistance direct voltage, transforms these pressure fluctuations into an alternating voltage, which is a measure of the isotopic composition of breath carbon dioxide.

- Sample Inlet

A semi-automatic sample inlet system injects the measuring gas in definite amounts into the zero gas circulating in the gas circuit of the infrared spectrometer. This enables measurement of the $^{13}C/^{12}C$-ratio at any CO_2 concentration above 1 %.

- Specifications for determining $^{13}C/^{12}C$-ratios

The breath test concept is based upon the oral administration of ^{13}C-labelled urea whose enzymatic hydrolysis is monitored by measuring $^{13}CO_2$ in breath using non-dispersive infrared spectrometry.

- Infrared spectrometers for breath analysis must comply with the following specifications:

Multiple replicate analyses: Minimum of 3 replicate analyses of the same sample during operation

Security access:	Storing of operating parameters and of results under security access to avoid later manipulation

For verifying the specifications linearity, stability, and precision of measurement have to be tested.

Zero point adjustment of the detectors by means of the zero gas generated in the spectrometer. End-point adjustment of the detectors by means of calibration gases of precisely known concentration.

Linearity:	≤ 0.5 ‰ for breath samples varying between 1 % and 7 % CO_2-concentration
Stability:	≤ 0.3 ‰ at 10 consecutive pulses
Precision of measurement:	≤ 0.5 ‰ for ^{13}C at natural abundance using a 100 ml breath bag with 3 % CO_2 breath concentration

Helicobacter pylori infection is present if the difference in $^{13}C/^{12}C$ of baseline-value and 30-minute-value exceeds 4.0 ‰**.**

Alternatively, any other suitable-validated method may be used, carried out by any objectively qualified laboratory.

Mass spectrometry (IRMS)

The breath samples, collected in 10 ml glass- or plastic sample tubes, are analysed by isotope ratio mass spectrometry (IRMS).

The analysis of the $^{13}C/^{12}C$-ratio in carbon dioxide of breath is an integrated part of the diagnostic test Helicobacter Test INFAI. The accuracy of the test strongly depends on the quality of the breath analysis. The specification of breath analysis parameters like linearity, stability (reference gas precision), and precision of measurement are fundamental for the accuracy of the system.

It has to be ensured that the analysis is carried out by a qualified laboratory. The method validated in the application is as follows:

- Sample preparation for (IRMS)

To determine the $^{13}C/^{12}C$-ratio of carbon dioxide in breath by mass spectrometric analysis the carbon dioxide must be separated from the breath and introduced into the mass spectrometer. The automatic preparation system for isotope mass spectrometers which is dedicated for breath test analysis is based on a gas-chromatographic continuous flow separation technique.

Water is removed from the sample by means of a Nafion water trap or the gas-chromatographic preparation system that separates the individual gases in a gas chromatographic column with Helium as eluent. Passing the column the separated gas species of breath are detected by an ionisation detector. The fraction of carbon dioxide gas, identified by its characteristic retention time, is introduced into mass spectrometer.

- Mass spectrometric analysis

To analyse the separated carbon dioxide sample gas its molecules must be ionised, formed into a beam, accelerated by an electric field, deflected in a magnetic field, and finally detected. These five processes take place in the analyser of a mass spectrometer, which consists of three separate sections: the source, flight tube, and collector. Ionisation, beam formation and acceleration all occur in the source, magnetic deflection takes place in the flight tube and detection takes place in the collector.

- Sample inlet

For introduction of the carbon dioxide into the analyser many sample inlet systems are available. For breath test analysis the individual balancing of the carbon dioxide of the sample to a reference standard gas is essential. This ensures the high accuracy of this system, as calculation of the isotopic content in carbon dioxide is done with respect to an independent standard.

- Specifications for determining $^{13}C/^{12}C$-ratios

The breath test concept relies on the administration of a specifically ^{13}C-labelled urea whose metabolite utilisation is monitored by measuring $^{13}CO_2$ in the expired breath gas.

- The mass spectrometer must be capable of:

Multiple replicate analyses:	Minimum of 3 replicate analyses of the same sample during operation
Security access:	Storing of operating parameters and of results under security access to avoid later manipulation
Adjustment:	$^{13}C/^{12}C$-ratio with respect to Pee Dee Beliminate (PDB)
Sample loop:	< 200 µl

The principal tests to verify the specifications are linearity, stability (reference gas precision), and precision of measurement.

- All mass spectrometers for breath analysis must comply with the following specifications:

Linearity:	≤ 0.5 ‰ for breath samples varying between 1 % and 7 % CO_2-concentration
Stability:	≤ 0.2 ‰ on 10 consecutive pulses
Precision of measurement:	≤ 0.3 ‰ for ^{13}C at natural abundance using a 10 ml breath sample tube with 3 % CO_2 breath concentration

Helicobacter pylori infection is present if the difference in $^{13}C/^{12}C$ of baseline-value and 30-minute-value exceeds 4.0 ‰.

Alternatively, any other suitable-validated method may be used, carried out by any objectively qualified laboratory.

7. MARKETING AUTHORISATION HOLDER

INFAI GmbH
Riehler Str. 36
D-50668 Köln
Germany

8. MARKETING AUTHORISATION NUMBERS

EU/1/97/045/005

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 14 August 1997
Date of latest renewal: 14 August 2007

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

INFAI GmbH
An der Kohlenbahn 39
D-58135 Hagen
Germany

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription.

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic Safety Update Reports**

The marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk Management Plan (RMP)**

Not applicable.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON, PACK OF 1 JAR AND 50 JARS

1. NAME OF THE MEDICINAL PRODUCT

Helicobacter Test INFAI 75 mg powder for oral solution
^{13}C-urea

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 jar containing 75 mg ^{13}C-urea.

3. LIST OF EXCIPIENTS

None

4. PHARMACEUTICAL FORM AND CONTENTS

Powder for oral solution

1 diagnostic test kit contains:
1 jar containing 75 mg ^{13}C-urea powder for oral solution
4 containers for breath samples
1 bendable straw
Package leaflet
Data sheet for patient documentation
Page of labels and sticker

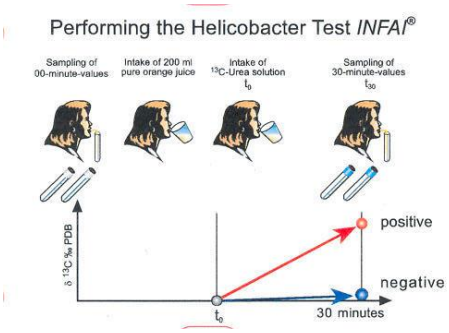
1 diagnostic test kit contains:
1 jar containing 75 mg ^{13}C-urea powder for oral solution
2 breath bags for breath samples
1 bendable straw
Package leaflet
Data sheet for patient documentation
Bar code labels and sticker

1 diagnostic test kit contains:
50 jars containing 75 mg ^{13}C-urea powder for oral solution
100 breath bags for breath samples
50 bendable straws
50 Package leaflet
50 Data sheets for patient documentation
50 Barcode labels and sticker

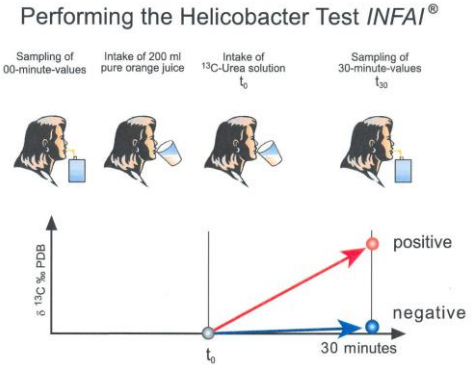
5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use

For Mass Spectrometry



For Infrared Spectroscopy



Please read enclosed instructions for use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP: {MM/YYYY}

9. SPECIAL STORAGE CONDITIONS

Do not store above 25°C.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Marketing Authorisation Holder:
INFAI GmbH
Riehler Str. 36
D-50668 Köln
Germany

12. MARKETING AUTHORISATION NUMBER(S)

Marketing Authorisation Number:
EU/1/97/045/001
EU/1/97/045/002
EU/1/97/045/004

13. BATCH NUMBER

Batch:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Helicobacter Test INFAI 75 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

INTERMEDIATE CARTON, PACK SIZE 50

1. NAME OF THE MEDICINAL PRODUCT

Helicobacter Test INFAI 75 mg powder for oral solution
^{13}C-urea

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 jar containing 75 mg ^{13}C-urea

3. LIST OF EXCIPIENTS

None

4. PHARMACEUTICAL FORM AND CONTENTS

Powder for oral solution

CLINIPAC 50

50 jars containing 75 mg ^{13}C-urea powder for oral solution

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP: {MM/YYYY}

9. SPECIAL STORAGE CONDITIONS

Do not store above 25°C.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

INFAI GmbH
Riehler Str. 36
D-50668 Köln
Germany

12. MARKETING AUTHORISATION NUMBER(S)

Marketing Authorisation Number:
EU/1/97/045/004

13. BATCH NUMBER

Batch:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Helicobacter Test INFAI 75 mg

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

JAR LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Helicobacter Test INFAI 75 mg powder for oral solution
^{13}C-urea
Oral use

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP: {MM/YYYY}

4. BATCH NUMBER

Batch:

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

Jar contains 75 mg ^{13}C-rea

6. OTHER

Single test
Powder for oral solution
Please read enclosed instructions for use.
Keep out of the sight and reach of children.
Do not store above 25 °C.
Medicinal product subject to medical prescription.
Marketing Authorisation Number:
EU/1/97/045/001
EU/1/97/045/002

INFAI GmbH
Riehler Str. 36
D-50668 Köln
Germany

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Helicobacter Test INFAI for children of the age 3-11 45 mg powder for oral solution
^{13}C-urea

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 jar containing 45 mg ^{13}C-urea.

3. LIST OF EXCIPIENTS

None

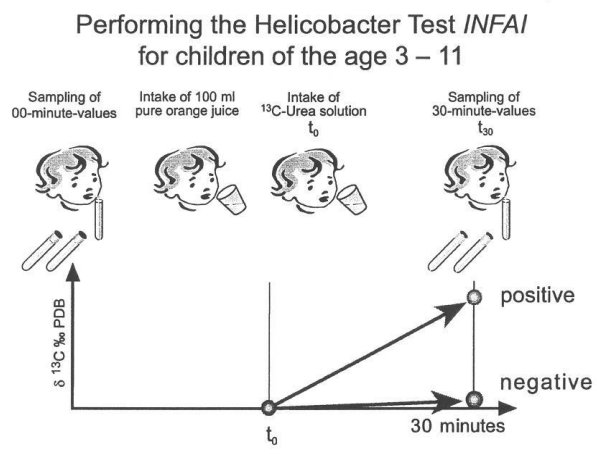
4. PHARMACEUTICAL FORM AND CONTENTS

Powder for oral solution
1 diagnostic test kit contains:
1 jar containing 45 mg ^{13}C-urea powder for oral solution
4 containers for breath samples
1 bendable straw
Package leaflet
Data sheet for patient documentation
Page of labels and sticker

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use

Please read the package leaflet before use.



6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP: {MM/YYYY}

9. SPECIAL STORAGE CONDITIONS

Do not store above 25°C.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Marketing Authorisation Holder:
INFAI GmbH
Riehler Str. 36
D-50668 Köln
Germany

12. MARKETING AUTHORISATION NUMBER(S)

Marketing Authorisation Number:
EU/1/97/045/003

13. BATCH NUMBER

Batch:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Helicobacter Test INFAI 45 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

JAR LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Helicobacter Test INFAI for children of the age 3-11 45 mg powder for oral solution
^{13}C-urea
Oral use

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP: {MM/YYYY}

4. BATCH NUMBER

Batch:

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

Jar contains 45 mg ^{13}C-urea

6. OTHER

Single test
Powder for oral solution
Please read enclosed instructions for use.
Keep out of the sight and reach of children.
Do not store above 25 °C.
Medicinal product subject to medical prescription.
Marketing Authorisation Number:
EU/1/97/045/003

INFAI GmbH
Riehler Str. 36
D-50668 Köln
Germany

MINIMUM PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

BREATH SAMPLE CONTAINERS: GLASS OR PLASTIC

1. NAME OF THE MEDICINAL PRODUCT

Helicobacter Test INFAI

2. NAME OF THE MARKETING AUTHORISATION HOLDER

INFAI GmbH
Riehler Str. 36
D-50668 Köln
Germany

3. EXPIRY DATE

4. BATCH NUMBER

5. OTHER

Breath sample container

00-minute value
30-minute value

Please stick round barcode label

MINIMUM PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

PAGE OF LABELS AND STICKERS

1. NAME OF THE MEDICINAL PRODUCT

Helicobacter Test INFAI

2. NAME OF THE MARKETING AUTHORISATION HOLDER

INFAI GmbH
Riehler Str. 36
D-50668 Köln
Germany

3. EXPIRY DATE

4. BATCH NUMBER

5. OTHER

Page of labels and sticker

Barcode for data sheet for patient documentation

Seal-Sticker

Barcodes for 00-minute-value
Barcodes for 30-minute-value

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON, PACK SIZE 50

1. NAME OF THE MEDICINAL PRODUCT

Helicobacter Test INFAI 75 mg powder for oral solution
^{13}C-urea

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 jar containing 75 mg ^{13}C-urea.

3. LIST OF EXCIPIENTS

None

4. PHARMACEUTICAL FORM AND CONTENTS

Powder for oral solution

CLINIPAC BASIC

50 jars containing 75 mg ^{13}C-urea powder for oral solution

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use

Please read enclosed instructions for use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP: {MM/YYYY}

9. SPECIAL STORAGE CONDITIONS

Do not store above 25°C.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Marketing Authorisation Holder:
INFAI GmbH
Riehler Str. 36
D-50668 Köln
Germany

12. MARKETING AUTHORISATION NUMBER(S)

Marketing Authorisation Number:
EU/1/97/045/005

13. BATCH NUMBER

Batch:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Helicobacter Test INFAI 75 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

INTERMEDIATE CARTON, PACK SIZE 50

1. NAME OF THE MEDICINAL PRODUCT

Helicobacter Test INFAI 75 mg powder for oral solution
^{13}C-urea

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 jar containing 75 mg ^{13}C-urea

3. LIST OF EXCIPIENTS

None

4. PHARMACEUTICAL FORM AND CONTENTS

Powder for oral solution

CLINIPAC BASIC

50 jars containing 75 mg ^{13}C-urea powder for oral solution

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP: {MM/YYYY}

9. SPECIAL STORAGE CONDITIONS

Do not store above 25°C.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

INFAI GmbH
Riehler Str. 36
D-50668 Köln
Germany

12. MARKETING AUTHORISATION NUMBER(S)

Marketing Authorisation Number:
EU/1/97/045/005

13. BATCH NUMBER

Batch:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Helicobacter Test INFAI 75 mg

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

JAR LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Helicobacter Test INFAI 75 mg powder for oral solution
^{13}C-urea
Oral use

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP: {MM/YYYY}

4. BATCH NUMBER

Batch:

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

Jar contains 75 mg ^{13}C-urea

6. OTHER

Single test
Powder for oral solution
Please read enclosed instructions for use.
Keep out of the sight and reach of children.
Do not store above 25 °C.
Medicinal product subject to medical prescription.
Marketing Authorisation Number:
EU/1/97/045/005

INFAI GmbH
Riehler Str. 36
D-50668 Köln
Germany

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Helicobacter Test INFAI 75 mg powder for oral solution
^{13}C-urea

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet:

1. What Helicobacter Test INFAI is and what it is used for

Helicobacter Test INFAI is for diagnostic use only. It is a breath test for adolescents from the age of 12 and adults to **determine the presence of bacterium Helicobacter pylori in the stomach**.

Why do you need to take the Helicobacter Test INFAI?
You may have a gastric infection caused by a bacterium called Helicobacter pylori. Your doctor has recommended that you have a Helicobacter Test INFAI for one of the following reasons:

- Your doctor wants to confirm whether you are suffering from Helicobacter pylori infection to help diagnose your condition.

- You have already been determined as being infected with Helicobacter pylori and have been taking medication aimed to clear up the infection. Your doctor now wishes to find out if the treatment has been successful.

How does the test work?
All foods contain a substance called carbon-13 (^{13}C). This carbon-13 can be detected in the carbon dioxide you breathe out of your lungs. The actual amount of carbon-13 in the breath will depend on the kind of food that you have eaten.

You will be asked to drink the “test meal”. Following the meal, samples of your breath will be taken. See “Special instructions for use”. These samples will be analysed to measure the “normal” amount of carbon-13 content in the carbon dioxide in your breath.

You will then be asked to drink a solution of carbon-13-urea. Further samples of your breath will then be taken 30 minutes later and the amount of carbon-13 in the samples measured as before. The results will be compared and a significant increase in the amount of carbon-13 in the second set of samples will suggest to your doctor that Helicobacter pylori is present.

2. What you need to know before you take Helicobacter Test INFAI

Do not take Helicobacter Test INFAI

- if you have or suspect that you have a **stomach infection** or a certain **inflammation of the stomach lining** (atrophic gastritis).
  This inflammation of the stomach lining may cause incorrect positive results of your breath test. Further investigations may be required to confirm the presence of Helicobacter pylori.

Warnings and precautions

Talk to your doctor or pharmacist before taking Helicobacter Test INFAI if you have any condition that can affect or be affected by the test.

Even if the result of Helicobacter Test INFAI is positive, further tests might be necessary before a treatment of a Helicobacter pylori infection may be started. These are required to check for the presence of any other complications, such as:

- stomach ulcer
- inflammation of the stomach lining caused by immune system
- tumours

There is insufficient data on the reliability of the Helicobacter Test INFAI for recommending its use in patients with removal of parts of the stomach.

If the patient vomits during the test procedure, repetition of the test is necessary. This should be done in fasted condition and not before the following day.

Other medicines and Helicobacter Test INFAI

Helicobacter Test INFAI is influenced by medicines influencing

- Helicobacter pylori (see section 3, second paragraph under “Method of use”)
- the enzyme urease, which stimulate the reduction of urea

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

Pregnancy and breast-feeding

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

It is not expected that performing the breath test during pregnancy and lactation has a damaging effect.

Driving and using machines

Helicobacter Test INFAI has no influence on the ability to drive or to use machines.

3. How to take Helicobacter Test INFAI

Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

You should perform the test in the presence of your doctor or another qualified person.

The recommended dose is

Patients from the age of 12 must take the content of one jar for one test.

Method of use

You must have fasted for 6 hours before application, preferably overnight. Ask your doctor, if fasting is a problem, for example for diabetic patients.

The test procedure lasts approximately 40 minutes.

The test should be performed following at least:
- 4 weeks after a therapy against a bacterial infection
- 2 weeks after the last administration of a medicine to reduce release of stomach acid

Both groups of medicines could influence the results of the Helicobacter Test INFAI. This is particularly after a therapy to remove Helicobacter pylori. It is important to follow the instructions for use exactly, otherwise the result may be questionable.

Essential items not supplied with Helicobacter Test INFAI
Before the breath test is performed a liquid test meal is taken to delay the stomach from emptying. The test meal is not provided within the kit. The following are suitable test meals:
- 200 ml 100 % orange juice or
- 1 g citric acid dissolved in 200 ml water

If you cannot take either of these test meals, please tell your doctor, who will suggest an alternative. A drinking vessel and tap water is required to dissolve the ^{13}C-urea powder. If the test needs to be repeated, this should be done on the following day at the earliest.

Special instructions for use (for mass spectrometry)
The test is to be performed after instruction by a healthcare professional and under appropriate medical supervision. The patient data should be documented using the provided data sheet. It is recommended that you take the test in a resting position.

1. The test should be carried out after having fasted 6 hours before application, preferably overnight. If the test needs to be carried out later in the day, only a light meal like tea and toast is recommended.
2. The test begins with the collection of samples for determining the baseline values:
   - The straw and sample tubes labelled “sampling time: 00-minute-value” are taken from the test set.
   - The stopper is removed from one of the sample containers and place the unwrapped straw into the container.
   - Now the patient breathes gently through the straw into the sample tube until the inside of the sample tube steams up.
   - The patient must continue to breathe through the straw while removing it from the sample tube, and then immediately seal the tube with its stopper.
     If the sample tube remains open for more than 30 seconds, the result could be inaccurate.
   - The sample container should be held upright and the bar-code label marked “00-minute-value” will be stuck round the sample container so that the lines of the bar code are horizontal.
3. Now the second sample container (labelled “sampling time: 00-minute-value”) has to be filled up with breath in the same way as described above.
4. Then the patient must drink the recommended test meal (200 ml 100 % orange juice or 1 g citric acid in 200 ml water).
5. Now the preparation of the test solution follows.
   - The jar labelled “^{13}C-urea powder” is removed from the test set, opened, and filled up to about three quarters with tap water.
   - The jar is closed and carefully shaken until all the powder has dissolved completely.
   - The contents are poured into a drinking glass, the jar filled a second and third time with water and the contents transferred into the drinking glass, so that approximately 30 ml of test solution is obtained.
6. The patient should drink this test solution immediately. The time of intake must be noted.
7. 30 minutes after the test solution has been taken (point 6), the “30-minute-value” samples are collected in both containers, which remain in the pack (labelled “sampling time: 30-minute-value”) as described under points 2 and 3.
   The bar-code labels marked “30-minute-value” must be used for these samples.

8. The corresponding bar-code label must be put on the data sheet for patient documentation. All breath sample containers should be placed back into the original packaging. This packaging should be sealed with the remaining sticker.
9. The package must be sent to a qualified laboratory for analysis.

Medical or healthcare professionals can find detailed information on the analysis of breath samples and the testing specifications for laboratories, in section 6.6 of the Summary of Product Characteristics.

If you take more Helicobacter Test INFAI than you should
Because only 75 mg ^{13}C-urea is provided overdose is not to be expected.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

No side effects are known.

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Helicobacter Test INFAI

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the label and carton after EXP. The expiry date refers to the last day of that month.

Do not store above 25°C.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Helicobacter Test INFAI contains
- The active substance is ^{13}C-urea.
  One jar contains 75 mg ^{13}C-urea.
- There are no other ingredients.

What Helicobacter Test INFAI looks like and contents of the pack
Helicobacter Test INFAI is a white, crystalline powder for oral solution.

Content of the test kit:

No.	Component	Quantity
1	Jar (10 ml volume, polystyrene with polyethylene snap cap) containing 75 mg ^{13}C-urea powder for oral solution	1
2	Labelled sample glass- or plastic- containers for sampling, storing and transporting the breath samples for analysis: Sampling time: 00-minute-value Sampling time: 30-minute-value	 2 2
3	Bendable straw for collection of the breath samples into the corresponding sample containers	1
4	Data sheet for patient documentation	1
5	Package leaflet	1
6	Page of barcode labels and sticker	1

Marketing Authorisation Holder
INFAI GmbH
Riehler Str. 36
D-50668 Köln
Germany

Manufacturer responsible for batch release
INFAI GmbH
An der Kohlenbahn 39
D-58135 Hagen
Germany

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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SL PLIVA LJUBLJANA d.o.o., Tel: +386 1 5890 390
HU, SK ALLMEDICAL s.r.o, Tel: +421 903 654 103, Szlovákia / Slovenská republika

This leaflet was last revised in MM/YYYY.

Detailed information on this medicine is available on the European Medicines Agency website: http://www.ema.europa.eu.

MINIMUM PARTICULARS TO APPEAR ON

DATA SHEET FOR PATIENT DOCUMENTATION

1. NAME OF THE MEDICINAL PRODUCT

Helicobacter Test INFAI

2. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

INFAI GmbH
Riehler Str. 36
D-50668 Köln
Germany

3. EXPIRY DATE

4. BATCH NUMBER

5. OTHER

Date of test

Patient ID

Date of birth

Barcode

Doctor/Hospital Address

Package leaflet: Information for the user

Helicobacter Test INFAI 75 mg powder for oral solution
^{13}C-urea

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet:

1. What Helicobacter Test INFAI is and what it is used for

Helicobacter Test INFAI is for diagnostic use only. It is a breath test for adolescents from the age of 12 and adults to **determine the presence of bacterium Helicobacter pylori in the stomach**.

Why do you need to take the Helicobacter Test INFAI?
You may have a gastric infection caused by a bacterium called Helicobacter pylori. Your doctor has recommended that you have a Helicobacter Test INFAI for one of the following reasons:

- Your doctor wants to confirm whether you are suffering from Helicobacter pylori infection to help diagnose your condition.

- You have already been determined as being infected with Helicobacter pylori and have been taking medication aimed to clear up the infection. Your doctor now wishes to find out if the treatment has been successful.

How does the test work?
All foods contain a substance called carbon-13 (^{13}C). This carbon-13 can be detected in the carbon dioxide you breathe out of your lungs. The actual amount of carbon-13 in the breath will depend on the kind of food that you have eaten.

You will be asked to drink the “test meal”. Following the meal, samples of your breath will be taken. See “Special instructions for use”. These samples will be analysed to measure the “normal” amount of carbon-13 content in the carbon dioxide in your breath.

You will then be asked to drink a solution of carbon-13-urea. Further samples of your breath will then be taken 30 minutes later and the amount of carbon-13 in the samples measured as before. The results will be compared and a significant increase in the amount of carbon-13 in the second set of samples will suggest to your doctor that Helicobacter pylori is present.

2. What you need to know before you take Helicobacter Test INFAI

Do not take Helicobacter Test INFAI

- if you have or suspect that you have a **stomach infection** or a certain **inflammation of the stomach lining** (atrophic gastritis).
  This inflammation of the stomach lining may cause incorrect positive results of your breath test. Further investigations may be required to confirm the presence of Helicobacter pylori.

Warnings and precautions

Talk to your doctor or pharmacist before taking Helicobacter Test INFAI if you have any condition that can affect or be affected by the test.

Even if the result of Helicobacter Test INFAI is positive, further tests might be necessary before a treatment of a Helicobacter pylori infection may be started. These are required to check for the presence of any other complications, such as:

- stomach ulcer
- inflammation of the stomach lining caused by immune system
- tumours

There is insufficient data on the reliability of the Helicobacter Test INFAI for recommending its use in patients with removal of parts of the stomach.

If the patient vomits during the test procedure, repetition of the test is necessary. This should be done in fasted condition and not before the following day.

Other medicines and Helicobacter Test INFAI

Helicobacter Test INFAI is influenced by medicines influencing

- Helicobacter pylori (see section 3, second paragraph under “Method of use”)
- the enzyme urease, which stimulate the reduction of urea

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

Pregnancy and breast-feeding

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

It is not expected that performing the breath test during pregnancy and lactation has a damaging effect.

Driving and using machines

Helicobacter Test INFAI has no influence on the ability to drive or to use machines.

3. How to take Helicobacter Test INFAI

Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

You should perform the test in the presence of your doctor or another qualified person.

The recommended dose is

Patients from the age of 12 must take the content of one jar for one test.

Method of use

You must have fasted for 6 hours before application, preferably overnight. Ask your doctor, if fasting is a problem, for example for diabetic patients.

The test procedure lasts approximately 40 minutes.

The test should be performed following at least:

- 4 weeks after a therapy against a bacterial infection
- 2 weeks after the last administration of a medicine to reduce release of stomach acid

Both groups of medicines could influence the results of the Helicobacter Test INFAI. This is particularly after a therapy to remove Helicobacter pylori. It is important to follow the instructions for use exactly, otherwise the result may be questionable.

Essential items not supplied with Helicobacter Test INFAI

Before the breath test is performed a liquid test meal is taken to delay the stomach from emptying. The test meal is not provided within the kit. The following are suitable test meals:

- 200 ml 100 % orange juice or
- 1 g citric acid dissolved in 200 ml water

If you cannot take either of these test meals, please tell your doctor, who will suggest an alternative. A drinking vessel and tap water is required to dissolve the ^{13}C-urea powder. If the test needs to be repeated, this should be done on the following day at the earliest.

Special instructions for use (for infrared spectroscopy)

The test is to be performed after instruction by a healthcare professional and under appropriate medical supervision. The patient data should be documented using the provided data sheet. It is recommended that you take the test in a resting position.

1. The test should be carried out after having fasted 6 hours before application, preferably overnight. If the test needs to be carried out later in the day, only a light meal like tea and toast is recommended.
2. The test begins with the collection of samples for determining the baseline values:
   - The straw and the breath bag labelled “sampling time: 00-minute-value” are taken from the test set.
   - The stopper is removed from the breath bag and place the unwrapped straw into the breath bag.
   - Now the patient breathes gently through the straw into the breath bag.
   - The patient must continue to breathe through the straw while removing it from the breath bag, and then immediately seal the breath bag with its stopper.
     If the breath bag remains open for more than 30 seconds, the result could be inaccurate.
   - The breath bag should be held upright and the bar-code label marked “00-minute-value” will be stuck on the breath bag.
3. Then the patient must drink the recommended test meal (200 ml 100 % orange juice or 1 g citric acid in 200 ml water).
4. Now the preparation of the test solution follows.
   - The jar labelled “^{13}C-urea powder” is removed from the test set, opened, and filled up to about three quarters with tap water.
   - The jar is closed and carefully shaken until all the powder has dissolved completely.
   - The contents are poured into a drinking glass, the jar filled a second and third time with water and the contents transferred into the drinking glass, so that approximately 30 ml of test solution is obtained.
5. The patient should drink this test solution immediately. The time of intake must be noted.
6. 30 minutes after the test solution has been taken (point 5), the “30-minute-value” sample is collected in the breath bag, which remains in the pack (labelled “sampling time: 30-minute-value”) as described under point 2.
   The bar-code label marked “30-minute-value” must be used for this sample.
7. The corresponding bar-code label must be put on the data sheet for patient documentation. All breath bags should be placed back into the original packaging. This packaging should be sealed with the remaining sticker.
8. The package must be sent to a qualified laboratory for analysis.

Medical or healthcare professionals can find detailed information on the analysis of breath samples and the testing specifications for laboratories, in section 6.6 of the Summary of Product Characteristics.

If you take more Helicobacter Test INFAI than you should
Because only 75 mg ^{13}C-urea is provided overdose is not to be expected.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

No side effects are known.

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Helicobacter Test INFAI

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the label and carton after EXP. The expiry date refers to the last day of that month.

Do not store above 25°C.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Helicobacter Test INFAI contains
- The active substance is ^{13}C-urea.
  One jar contains 75 mg ^{13}C-urea.
- There are no other ingredients.

What Helicobacter Test INFAI looks like and contents of the pack
Helicobacter Test INFAI is a white, crystalline powder for oral solution.

Content of the test kit with 1 jar:

No.	Component	Quantity
1	Jar (10 ml volume, polystyrene with polyethylene snap cap) containing 75 mg ^{13}C-urea powder for oral solution	1
2	Breath bags: Sampling time: 00-minute-value Sampling time: 30-minute-value	 1 1
3	Bendable straw for collection of the breath samples into the corresponding breath bags	1
4	Data sheet for patient documentation	1
5	Package leaflet	1
6	Page of barcode labels and sticker	1

Content of the test kit with 50 jars:

No.	Component	Quantity
1	Jar (10 ml volume, polystyrene with polyethylene snap cap) containing 75 mg ^{13}C-urea powder for oral solution	50
2	Breath bags: Sampling time: 00-minute-value Sampling time: 30-minute-value	 50 50
3	Bendable straw for collection of the breath samples into the corresponding breath bags	50
4	Data sheet for patient documentation	50
5	Package leaflet	50
6	Page of barcode labels and sticker	50

Marketing Authorisation Holder
INFAI GmbH
Riehler Str. 36
D-50668 Köln
Germany

Manufacturer responsible for batch release
INFAI GmbH
An der Kohlenbahn 39
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Germany

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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This leaflet was last revised in MM/YYYY.

Detailed information on this medicine is available on the European Medicines Agency website: http://www.ema.europa.eu.

MINIMUM PARTICULARS TO APPEAR ON

DATA SHEET FOR PATIENT DOCUMENTATION

1. NAME OF THE MEDICINAL PRODUCT

Helicobacter Test INFAI

2. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

INFAI GmbH
Riehler Str. 36
D-50668 Köln
Germany

3. EXPIRY DATE

4. BATCH NUMBER

5. OTHER

Date of test

Patient ID

Date of birth

Barcode

Doctor/Hospital Address

Package leaflet: Information for the user

Helicobacter Test INFAI for children of the age 3-11 45 mg powder for oral solution
^{13}C-urea

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet:

1. What Helicobacter Test INFAI for children of the age 3 to 11 is and what it is used for

Helicobacter Test INFAI for children of the age 3-11 is for diagnostic use only. It is a breath test for children aged 3-11 years to **determine the presence of bacterium Helicobacter pylori in the stomach or duodenum**.

Why do you need to take the Helicobacter Test INFAI for children of the age 3-11?
You may have a gastric or duodenum infection caused by a bacterium called Helicobacter pylori. Your doctor has recommended that you have a Helicobacter Test INFAI for children of the age 3-11 for one of the following reasons:

- Your doctor wants to confirm whether you are suffering from Helicobacter pylori infection to help diagnose your condition.

- You have already been determined as being infected with Helicobacter pylori and have been taking medication aimed to clear up the infection. Your doctor now wishes to find out if the treatment has been successful.

How does the test work?
All foods contain a substance called carbon-13 (^{13}C). This carbon-13 can be detected in the carbon dioxide you breathe out of your lungs. The actual amount of carbon-13 in the breath will depend on the kind of food that you have eaten.

You will be asked to drink the “test meal”. Following the meal, samples of your breath will be taken. See “Special instructions for use”. These samples will be analysed to measure the “normal” amount of carbon-13 content in the carbon dioxide in your breath.

You will then be asked to drink a solution of carbon-13-urea. Further samples of your breath will then be taken 30 minutes later and the amount of carbon-13 in the samples measured as before. The results will be compared and a significant increase in the amount of carbon-13 in the second set of samples will suggest to your doctor that Helicobacter pylori is present.

2. What you need to know before you take Helicobacter Test INFAI for children of the age 3-11

Do not take Helicobacter Test INFAI for children of the age 3-11

- if you have or suspect that you have a **stomach infection** or a certain **inflammation of the stomach lining** (atrophic gastritis).
  This inflammation of the stomach lining may cause incorrect positive results of your breath test. Further investigations may be required to confirm the presence of Helicobacter pylori.

Warnings and precautions

Talk to your doctor or pharmacist before taking Helicobacter Test INFAI for children of the age 3-11 if you have any condition that can affect or be affected by the test.

Even if the result of Helicobacter Test INFAI for children of the age 3-11 is positive, further tests might be necessary before a treatment of a Helicobacter pylori infection may be started. These are required to check for the presence of any other complications, such as:

- stomach ulcer
- inflammation of the stomach lining caused by immune system
- tumours

There is insufficient data on the reliability of the Helicobacter Test INFAI for children of the age 3-11 for recommending its use in patients with removal of parts of the stomach.

If the patient vomits during the test procedure, repetition of the test is necessary. This should be done in fasted condition and not before the following day.

O**ther medicines** and Helicobacter Test INFAI for children of the age 3**-11**

Helicobacter Test INFAI for children of the age 3-11 is influenced by medicines influencing

- Helicobacter pylori (see section 3, second paragraph under “Method of use”)
- the enzyme urease, which stimulate the reduction of urea

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

3. How to take Helicobacter Test INFAI for children of the age 3-11

Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

You should perform the test in the presence of your doctor or another qualified person.

The recommended dose is

Children aged 3-11 years must take the content of one jar for one test.

Method of use

You must have fasted for 6 hours before application, preferably overnight. Ask your doctor, if fasting is a problem, for example for diabetic patients.

The test procedure lasts approximately 40 minutes.

The test should be performed following at least:

- 4 weeks after a therapy against a bacterial infection
- 2 weeks after the last administration of a medicine to reduce release of stomach acid

Both groups of medicines could influence the results of the Helicobacter Test INFAI for children of the age 3-11. This is particularly after a therapy to remove Helicobacter pylori. It is important to follow the instructions for use exactly, otherwise the result may be questionable.

Essential items not supplied with Helicobacter Test INFAI for children of the age 3-11
Before the breath test is performed a liquid test meal is taken to delay the stomach from emptying. The test meal is not provided within the kit. The following is a suitable test meal:

- 100 ml 100 % orange juice

If you cannot take this test meal, please tell your doctor, who will suggest an alternative. A drinking vessel and tap water is required to dissolve the ^{13}C-urea powder. If the test needs to be repeated, this should be done on the following day at the earliest.

Special instructions for use (for mass spectrometry)
The test is to be performed after instruction by a healthcare professional and under appropriate medical supervision. The patient data should be documented using the provided data sheet. It is recommended that you take the test in a resting position.

1. The test should be carried out after having fasted 6 hours before application, preferably overnight. If the test needs to be carried out later in the day, only a light meal like tea and toast is recommended.
2. The test begins with the collection of samples for determining the baseline values:
   - The straw and sample tubes labelled “sampling time: 00-minute-value” are taken from the test set.
   - The stopper is removed from one of the sample containers and place the unwrapped straw into the container.
   - Now the patient breathes gently through the straw into the sample tube until the inside of the sample tube steams up.
   - The patient must continue to breathe through the straw while removing it from the sample tube, and then immediately seal the tube with its stopper.
     If the sample tube remains open for more than 30 seconds, the result could be inaccurate.
   - The sample container should be held upright and the bar-code label marked “00-minute-value” will be stuck round the sample container so that the lines of the bar code are horizontal.
3. Now the second sample container (labelled “sampling time: 00-minute-value”) has to be filled up with breath in the same way as described above.
4. Then the patient must drink the recommended test meal (100 ml 100 % orange juice).
5. Now the preparation of the test solution follows.
   - The jar labelled “^{13}C-urea powder” is removed from the test set, opened, and filled up to about three quarters with tap water.
   - The jar is closed and carefully shaken until all the powder has dissolved completely.
   - The contents are poured into a drinking glass, the jar filled a second and third time with water and the contents transferred into the drinking glass, so that approximately 30 ml of test solution is obtained.
6. The patient should drink this test solution immediately. The time of intake must be noted.
7. 30 minutes after the test solution has been taken (point 6), the “30-minute-value” samples are collected in both containers, which remain in the pack (labelled “sampling time: 30-minute-value”) as described under points 2 and 3.
   The bar-code labels marked “30-minute-value” must be used for these samples.
8. The corresponding bar-code label must be put on the data sheet for patient documentation. All breath sample containers should be placed back into the original packaging. This packaging should be sealed with the remaining sticker.
9. The package must be sent to a qualified laboratory for analysis.

Medical or healthcare professionals can find detailed information on the analysis of breath samples and the testing specifications for laboratories, in section 6.6 of the Summary of Product Characteristics.

If you take more Helicobacter Test INFAI for children of the age 3-11 than you should
Because only 45 mg ^{13}C-urea is provided overdose is not to be expected.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

No side effects are known.

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Helicobacter Test INFAI for children of the age 3-11

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the label and carton after EXP. The expiry date refers to the last day of that month.

Do not store above 25°C.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Helicobacter Test INFAI for children of the age 3-11contains
- The active substance is ^{13}C-urea.
  One jar contains 45 mg ^{13}C-urea.
- There are no other ingredients.

What Helicobacter Test INFAI for children of the age 3-11 looks like and contents of the pack
Helicobacter Test INFAI for children of the age 3-11 is a white, crystalline powder for oral solution.

Content of the test kit:

No.	Component	Quantity
1	Jar (10 ml volume, polystyrene with polyethylene snap cap) containing 45 mg ^{13}C-urea powder for oral solution	1
2	Labelled sample glass- or plastic containers for sampling, storing and transporting the breath samples for analysis: Sampling time: 00-minute-value Sampling time: 30-minute-value	 2 2
3	Bendable straw for collection of the breath samples into the corresponding sample containers	1
4	Data sheet for patient documentation	1
5	Package leaflet	1
6	Page of barcode labels and sticker	1

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Riehler Str. 36
D-50668 Köln
Germany

Manufacturer responsible for batch release
INFAI GmbH
An der Kohlenbahn 39
D-58135 Hagen
Germany

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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This leaflet was last revised in MM/YYYY.

Detailed information on this medicine is available on the European Medicines Agency website: http://www.ema.europa.eu.

MINIMUM PARTICULARS TO APPEAR ON

DATA SHEET FOR PATIENT DOCUMENTATION

1. NAME OF THE MEDICINAL PRODUCT

Helicobacter Test INFAI

2. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

INFAI GmbH
Riehler Str. 36
D-50668 Köln
Germany

3. EXPIRY DATE

4. BATCH NUMBER

5. OTHER

Date of test

Patient ID

Date of birth

Barcode

Doctor/Hospital Address

Package leaflet: Information for the user

Helicobacter Test INFAI 75 mg powder for oral solution
CliniPac Basic
without breath sample containers
^{13}C-urea

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet:

1. What Helicobacter Test INFAI is and what it is used for

Helicobacter Test INFAI is for diagnostic use only. It is a breath test for adolescents from the age of 12 and adults to **determine the presence of bacterium Helicobacter pylori in the stomach**.

Why do you need to take the Helicobacter Test INFAI?
You may have a gastric infection caused by a bacterium called Helicobacter pylori. Your doctor has recommended that you have a Helicobacter Test INFAI for one of the following reasons:

- Your doctor wants to confirm whether you are suffering from Helicobacter pylori infection to help diagnose your condition.

- You have already been determined as being infected with Helicobacter pylori and have been taking medication aimed to clear up the infection. Your doctor now wishes to find out if the treatment has been successful.

How does the test work?
All foods contain a substance called carbon-13 (^{13}C). This carbon-13 can be detected in the carbon dioxide you breathe out of your lungs. The actual amount of carbon-13 in the breath will depend on the kind of food that you have eaten.

You will be asked to drink the “test meal”. Following the meal, samples of your breath will be taken. See “Special instructions for use”. These samples will be analysed to measure the “normal” amount of carbon-13 content in the carbon dioxide in your breath.

You will then be asked to drink a solution of carbon-13-urea. Further samples of your breath will then be taken 30 minutes later and the amount of carbon-13 in the samples measured as before. The results will be compared and a significant increase in the amount of carbon-13 in the second set of samples will suggest to your doctor that Helicobacter pylori is present.

2. What you need to know before you take Helicobacter Test INFAI

Do not take Helicobacter Test INFAI
- if you have or suspect that you have a **stomach infection** or a certain **inflammation of the stomach lining** (atrophic gastritis).
  This inflammation of the stomach lining may cause incorrect positive results of your breath test. Further investigations may be required to confirm the presence of Helicobacter pylori.

Warnings and precautions
Talk to your doctor or pharmacist before taking Helicobacter Test INFAI if you have any condition that can affect or be affected by the test.

Even if the result of Helicobacter Test INFAI is positive, further tests might be necessary before a treatment of a Helicobacter pylori infection may be started. These are required to check for the presence of any other complications, such as:
- stomach ulcer
- inflammation of the stomach lining caused by immune system
- tumours

There is insufficient data on the reliability of the Helicobacter Test INFAI for recommending its use in patients with removal of parts of the stomach.

If the patient vomits during the test procedure, repetition of the test is necessary. This should be done in fasted condition and not before the following day.

Other medicines and Helicobacter Test INFAI
Helicobacter Test INFAI is influenced by medicines influencing
- Helicobacter pylori (see section 3, second paragraph under “Method of use”)
- the enzyme urease, which stimulate the reduction of urea

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

Pregnancy and breast-feeding
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.
It is not expected that performing the breath test during pregnancy and lactation has a damaging effect.

Driving and using machines
Helicobacter Test INFAI has no influence on the ability to drive or to use machines.

3. How to take Helicobacter Test INFAI

Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

You should perform the test in the presence of your doctor or another qualified person.

The recommended dose is
Patients from the age of 12 must take the content of one jar for one test.

Method of use
You must have fasted for 6 hours before application, preferably overnight. Ask your doctor, if fasting is a problem, for example for diabetic patients.

The test procedure lasts approximately 40 minutes.

The test should be performed following at least:

- 4 weeks after a therapy against a bacterial infection
- 2 weeks after the last administration of a medicine to reduce release of stomach acid

Both groups of medicines could influence the results of the Helicobacter Test INFAI. This is particularly after a therapy to remove Helicobacter pylori. It is important to follow the instructions for use exactly, otherwise the result may be questionable.

Essential items not supplied with Helicobacter Test INFAI

Before the breath test is performed a liquid test meal is taken to delay the stomach from emptying. The test meal is not provided within the kit. The following are suitable test meals:

- 200 ml 100 % orange juice or
- 1 g citric acid dissolved in 200 ml water

If you cannot take either of these test meals, please tell your doctor, who will suggest an alternative. A drinking vessel and tap water is required to dissolve the ^{13}C-urea powder. If the test needs to be repeated, this should be done on the following day at the earliest.

Special instructions for use (for infrared spectroscopy or mass spectrometry)

The test is to be performed after instruction by a healthcare professional and under appropriate medical supervision. The patient data should be documented using the provided data sheet. It is recommended that you take the test in a resting position.

1. The test should be carried out after having fasted 6 hours before application, preferably overnight. If the test needs to be carried out later in the day, only a light meal like tea and toast is recommended.
2. For mass spectrometric analysis, please use sample tubes for collection the breath samples; for infrared spectroscopy, use breath bags. Both are not included in the package.
3. The test begins with the collection of samples for determining the baseline values:
    - Use the straw and the breath sample container described under point 2 labelled “sampling time: 00-minute-value”.
    - The stopper is removed from one of the breath sample containers described under point 2 and place the unwrapped straw into the breath sample container.
    - Now the patient breathes gently through the straw into the breath sample container.
    - The patient must continue to breathe through the straw while removing it from the breath sample container, and then immediately seal the breath sample container with its stopper. If the breath sample container remains open for more than 30 seconds, the result could be inaccurate.
    - The breath sample container should be held upright and the bar-code label marked “00-minute-value” will be stuck on the breath sample container.
4. Now the second breath sample container (labelled “sampling time: 00-minute-value”) has to be filled up with breath in the same way as described above. The second breath sample container is only required for mass spectrometry. For infrared spectroscopy, only one breath bag is required.
5. Then the patient must drink the recommended test meal (200 ml 100 % orange juice or 1 g citric acid in 200 ml water).
6. Now the preparation of the test solution follows.
    - The jar labelled “^{13}C-urea powder” is removed from the pack, opened, and filled up to about three quarters with tap water.
    - The jar is closed and carefully shaken until all the powder has dissolved completely.
    - The contents are poured into a drinking glass, the jar filled a second and third time with water and the contents transferred into the drinking glass, so that approximately 30 ml of test solution is obtained.
7. The patient should drink this test solution immediately. The time of intake must be noted.
8. 30 minutes after the test solution has been taken (point 7), the “30-minute-value” samples are collected in the breath sample containers labelled “sampling time: 30-minute-value” as described under point 3 and 4.
   The bar-code labels marked “30-minute-value” must be used for these samples.

9. The corresponding bar-code label must be put on the data sheet for patient documentation.
10. All breath sample containers and the patient documentation must be sent to a qualified laboratory for analysis.

Medical or healthcare professionals can find detailed information on the analysis of breath samples and the testing specifications for laboratories, in section 6.6 of the Summary of Product Characteristics.

If you take more Helicobacter Test INFAI than you should
Because only 75 mg ^{13}C-urea is provided overdose is not to be expected.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

No side effects are known.

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Helicobacter Test INFAI

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the label and carton after EXP. The expiry date refers to the last day of that month.

Do not store above 25°C.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Helicobacter Test INFAI contains
- The active substance is ^{13}C-urea.
  One jar contains 75 mg ^{13}C-urea.
- There are no other ingredients.

What Helicobacter Test INFAI looks like and contents of the pack
Helicobacter Test INFAI is a white, crystalline powder for oral solution.

Content of the test kit with 50 jars:

No.	Component	Quantity
1	Jar (10 ml volume, polystyrene with polyethylene snap cap) containing 75 mg ^{13}C-urea powder for oral solution	50
2	Data sheet for patient documentation	50
3	Package leaflet	50
4	Barcode labels and stickers	50

Marketing Authorisation Holder
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D-50668 Köln
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Manufacturer responsible for batch release
INFAI GmbH
An der Kohlenbahn 39
D-58135 Hagen
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For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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MINIMUM PARTICULARS TO APPEAR ON

DATA SHEET FOR PATIENT DOCUMENTATION

1. NAME OF THE MEDICINAL PRODUCT

Helicobacter Test INFAI

2. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

INFAI GmbH
Riehler Str. 36
D-50668 Köln
Germany

3. EXPIRY DATE

4. BATCH NUMBER

5. OTHER

Date of test

Patient ID

Date of birth

Barcode

Doctor/Hospital Address