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Datasheet for the decision of 10 September 2015

Case Number: T 2400/12 - 3.3.07

Application Number: 01930187.8

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Language of the proceedings: EN

Title of invention:
PREPARATIONS FOR DIAGNOSING INFECTION WITH HELICOBACTER PYLORI

Patent Proprietor:
OTSUKA PHARMACEUTICAL CO., LTD.

Opponent:
Orexo AB

Headword:
PREPARATIONS FOR DIAGNOSING INFECTION WITH HELICOBACTER PYLORI/Otsuka Pharmaceutical Co., LTD

Relevant legal provisions:
EPC Art. 56

Keyword:
Inventive step - All requests (no)
Inventive step - obvious alternative

Decisions cited:

Catchword:

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Beschwerdekammern
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Chambres de recours

European Patent Office
D-80298 MUNICH
GERMANY
Tel. +49 (0) 89 2399-0
Fax +49 (0) 89 2399-4465

Case Number: T 2400/12 - 3.3.07

D E C I S I O N
of Technical Board of Appeal 3.3.07
of 10 September 2015

Appellant: (Opponent)	Orexo AB Box 303 751 05 Uppsala (SE)
Representative:	Potter Clarkson LLP The Belgrave Centre Talbot Street Nottingham, NG1 5GG (GB)
Respondent: (Patent Proprietor)	OTSUKA PHARMACEUTICAL CO., LTD. 9, Kandatsukasa-cho 2-chome Chiyoda-ku Tokyo 101-8535 (JP)
Representative:	Hoffmann Eitle Patent- und Rechtsanwälte PartmbB Arabellastraße 30 81925 München (DE)
Decision under appeal:	**Decision of the Opposition Division of the European Patent Office posted on 30 October 2012 rejecting the opposition filed against European patent No. 1283060 pursuant to Article 101(2) EPC.**

Composition of the Board:

Chairman	J. Riolo
Members:	D. Boulois
	D. T. Keeling

Summary of Facts and Submissions

I. European patent No. 1 283 060 based on application No. 01 930 187.8 was granted on the basis of a set of 16 claims.

Independent claim 1 as granted read as follows:

"1. A coated preparation for use in the detection of *Helicobacter pylori* infection comprising:

(i) a core composition comprising:

19 to 89 parts by weight of isotope carbon-labeled urea relative to 100 parts by weight of the core composition,

10 to 80 parts by weight of an excipient component relative to 100 parts by weight of the core composition and,

0.01 to 1 parts by weight of a lubricant component relative to 100 parts by weight of the core composition,

the excipient component comprising:

(a) at least one member selected from the group consisting of lactose, sucrose and glucose,

(b) at least one member selected from the group consisting of crystalline cellulose, low-substitution hydroxypropylcellulose, carboxymethylcellulose calcium and croscarmellose sodium, and

(c) at least one member selected fron the group consisting of starch, carboxymethylstarch sodium, hydroxypropylstarch, and partially pregelatinized starch; and

(ii) a coating agent, the core composition being coated with 0.1 to 5parts by weight of the coating agent

relative to 100 parts by weight of the core composition."

II. An opposition was filed under Article 100 (a), (b), (c) on the grounds that the subject-matter of the patent lacked novelty, inventive step and industrial applicability, the patent was not sufficiently disclosed and its subject-matter extended beyond the content of the application as filed.

III. The documents cited during the opposition proceedings included the following:
(1): WO 06/14091
(5): EP A 0 860 170
(7): Aulton, 1988, "Pharmaceutics; The Science of dosage form design"
(10): Data submitted on 13.9.2007
(11): Data submitted with the statement of opposition

IV. The present appeal by the opponents lies from the decision of the opposition division to reject the opposition. The decision was based on the claims as granted.

V. According to the decision under appeal, the claims were considered to meet the requirements of Article 123(2) EPC. A clear pointer to a core of three excipients and their coating with 0.1 to 5 parts by weight of coating agent was found on pages 14 and 15 of the original description.
The skilled person would understand what the term "coating agent" means, and thus the requirements of disclosure and industrial applicability were met.
As regards inventive step, document (5) was the closest prior art, since it disclosed tablets of labelled urea for diagnosing H. pylori. The labelled urea was

converted to CO2 in the stomach by H. pylori, which could be detected in the breath of the patient. The problem addressed by document (5) was the elimination of false positives due to the degradation in the oral cavity and not in the stomach. This was achieved by a tablet designed to disintegrate only in the stomach, from which the claimed subject-matter of the contested patent differed in the presence of a coating and of three excipients. The problem to be solved was the provision of an alternative solution to that of document (5). The solution was the presence of a coating and three specified core excipients. Although document (5) stated that a coating might be present, it gave no indication of its necessity, or that the coating could be used advantageously to allow the tailoring of the three core excipients to provide an alternative solution to the problem of false positives. Document (7) related to taste masking coating, and documents (10) and (11) showed that the selection of core excipients had a considerable effect in disintegration times.
The claims as granted were regarded as meeting the requirements of Article 56 EPC.

VI. The opponent (appellant) filed an appeal against said decision.

VII. With a letter dated 4 September 2013 the respondent submitted 8 auxiliary requests and *inter alia* the following piece of evidence:
(12): Description of a Disintegration/Dissolution Test comparing the preparations according to EP 1 283 060 B1 with those of references D1 and D5

VIII. With a letter dated 1 April 2014, the appellant submitted *inter alia* the following evidence:

(18): Exhibit B – "A Novel Tablet-Based 13C Urea Breath Test For Helicobacter pylori with Enhanced Performance during Acid Suppression Therapy", A. Hamlet et al, Scand. J. Gastroenterol., 1999(4), pages 368-374

IX. On 24 July 2015 the Board sent a communication to the parties, stating in particular its preliminary opinion, that, in the absence of any evidence relating to an improved effect, the problem was the provision of an alternative dosage form and that the solution proposed appeared to be obvious in view of the disclosure of document (5).

X. Oral proceedings took place on 17 September 2015. During oral proceedings,the respondent filed a new main request and auxiliary requests 1-4 corresponding respectively to auxiliary requests 3 and 5-8 filed previously.

The subject-matter of the independent claims 1 of the requests read as follows, the difference(s) compared with the main request maintained by the opposition division shown in bold:

(a) Main request

"1. A coated preparation for use in the detection of *Helicobacter pylori* infection comprising:
(i) a core composition comprising:
19 to 89 parts by weight of isotope carbon-labeled urea relative to 100 parts by weight of the core composition,
10 to 80 parts by weight of an excipient component relative to 100 parts by weight of the core composition and,

0.01 to 1 parts by weight of a lubricant component relative to 100 parts by weight of the core composition,

the excipient component comprising:

(a) at least one member selected from the group consisting of lactose, sucrose and glucose,

(b) at least one member selected from the group consisting of crystalline cellulose, ~~**low-substitution hydroxypropylcellulose,**~~ carboxymethylcellulose calcium and croscarmellose sodium, and

(c) at least one member selected from the group consisting of starch, carboxymethylstarch sodium, hydroxypropylstarch, and partially pregelatinized starch; and

(ii) a coating agent, **comprising a water-soluble polymer, which is at least one member of the group consisting of pullulan, dextrin, alkali metal alginate, hydroxypropylcellulose, hydroxypropylmethylcellulose, methylcellulose and polyvinylpyrrolidone and**

the core composition being coated with 0.1 to 5parts by weight of the coating agent relative to 100 parts by weight of the core composition."

(b) Auxiliary request 1

"1. A coated preparation for use in the detection of *Helicobacter pylori* infection comprising:

(i) a core composition comprising:

19 to 89 parts by weight of isotope carbon-labeled urea relative to 100 parts by weight of the core composition,

10 to 80 parts by weight of an excipient component relative to 100 parts by weight of the core composition and,

0.01 to 1 parts by weight of a lubricant component relative to 100 parts by weight of the core composition,
wherein the core composition contains lactose, crystalline cellulose and starch as the excipient component and magnesium stearate as the lubricant component, and
(ii) a coating agent, **comprising hydroxypropylmethylcellulose, polyethylene glycol, titanium oxide and talc and**
the core composition being coated with 0.1 to 5parts by weight of the coating agent relative to 100 parts by weight of the core composition."

(c) Auxiliary request 2

The subject-matter of claim 1 of auxiliary request 2 corresponds to the subject-matter of claim 1 of auxiliary request 1 with the following restriction shown in bold:
"the core composition being coated with **0.3** to 5parts by weight of the coating agent relative to 100 parts by weight of the core composition."

(c) Auxiliary request 3

"1. A coated preparation for use in the detection of *Helicobacter pylori* infection comprising:
(i) a core composition comprising:
30-70 weight% of isotope carbon-labeled urea,
35-65 by weight% of an excipient component and,
0.1-0.7 weight% of a lubricant component,
based on 100% of the core composition,
wherein the core composition contains lactose, crystalline cellulose and starch as the excipient

component and magnesium stearate as the lubricant component, and

(ii) a coating agent, **comprising hydroxypropylmethylcellulose, polyethylene glycol, titanium oxide and talc and**

the core composition being coated with **0.3** to 5parts by weight of the coating agent relative to 100 parts by weight of the core composition."

(d) Auxiliary request 4

"1. A coated preparation for use in the detection of *Helicobacter pylori* infection comprising:

(i) a core composition comprising:

50 weight% of ^{13}C-labeled urea,

17.2 weight% of lactose

30.0 weight% of crystalline cellulose

2.5 weight% of corn starch and

0.3 weight% of magnesium stearate;

and

(ii) a coating agent **consisting of 60 weight% of hydroxypropyl methylcellulose, 20 weight% of polyethylene glycol, 10 weight% of titanium oxide and 10 weight% of tal,**

wherein the coating agent is present in an amount of **2 parts by weight** based on 100 parts by weight of the core composition."

XI. The arguments of the appellant may be summarized as follows:

Document (1) and (5) could be considered as potential closest state of the art. As regards document (5), it disclosed tablets for the urea breath tests by detection of *H. pylori*, which were optionally provided with a quick soluble coating (see page 4, line 6). It

included saccharides, cellulose derivatives and starch derivatives as excipients (see pages 2 and 3). Figure 1 of document (5) showed that the tablets disclosed therein had the same effect than the composition of the invention claimed by the main request.
The differences between the claimed invention and document (5) were the essential presence of a coating in a specific amount and the necessity to include all three of the saccharides, cellulose and starch components. There was no limitation in claim 1 of the main request about a quick disintegration time of the core component so that this feature could not be taken in consideration.
The problem to be solved could not realistically be the provision of a urea breath test that is improved because it was free from the risk of false positive test results resulting from urease-producing bacteria in the oral cavity. This was because document (5) presented clinical data showing that the exemplified tablets also solved that very problem (see document (5), Test example 4 and Table 5). These data were similar to the data given in Table 5 and Figure 1 of the contested patent. The problem was therefore seen as the provision of an alternative composition.
The solution was obvious, since all claimed components were disclosed in document (5), such as in examples 4-7. Moreover, document (6) showed that all the excipients were common as diluents, binding agents and disintegrating agents (see document (6), page 325-328). The skilled person would have substituted any of lactose, cellulose or starch with an equivalent known excipient. As regards the coating, document (7) showed that the use of a coating based on hydroxypropylmethyl cellulose was common general knowledge, in particular in combination with PEG and colorants.

Document (11) showed a composition comprising only some of the claimed excipients, which showed a short disintegration time. It was a evidence that compositions comprising a core such as in document (5) would provide the same disintegration time. As regards the data of document (12), it was self evident that the provision of a coating would slow the dissolution of a tablet.

As regards inventive step of auxiliary request 1, there was no limitation in claim 1 on the disintegration time of the core component of the composition; the core composition was thus not limited to a quick disintegrating composition but included also slow release compositions. Moreover, Table 3 of document (5) showed tablets with a disintegration time of less than than one minute. The problem had to be posed as the provision of alternative compositions, as for the main request, and the solution was obvious for the same reasons.

The arguments were the same for the other auxiliary requests.

XII. The arguments of the respondent may be summarized as follows

Document (5) was considered as the closest state of the art. In this document, the disintegration time was linked with the hardness of the tablets (see page 3, line 38). The document did not give any indication about the type or amount of coating wich could be used, and also nothing on the possible purpose of said coating. In this document, a compromise had to be made between a fast disintegration time and a disintegration with a long lag time. Example 3 and Table 4 of document

(5) showed that the disintegration time varied enormously. As regards Table 5 of document (5), there was no information on the hardness and disintegration time of the tablet used therein. The difference between the claimed preparation and the tablets of document (5) was the presence of a coating and the specific excipients of the core component. The effect was seen as the provision of a composition which dissolved quickly n the stomach and did not dissolve in the mouth.

In the written proceedings, the problem was seen as the provision of a composition which minimized the risk of a false positive result while still obtaining a suitable response within the appropriate time limit and simultaneously allowing a greater freedom with regard to the choice of excipient. Document (12) was provided to show the existence of an effect. The water dissolution performed in document (12) compared the dissolution of a coated according to the invention and an uncoated tablets according to document (5). Coated tablets according to the invention were protected from the dissolution by their coating, while uncoated tablets started to dissolve after one second already. This document was a reproduction of the what occurred in the oral cavity. Consequently, there was a risk of false positive results if the uncoated preparations of document (5) were taken by a person to be tested, if the preparation had not be swallowed immediately. The solution was not obvious, since no prior taught or suggested that this problem could have been solved by the simultaneous use of a coating and a quick dissolving core.

In the case that the problem should have been reformulated as the provision of an alternative

composition for the diagnosis of *H. pylori*, the problem would not have been the provision of any alternative preparation, but to provide an alternative preparation that is capable of diagnosing an *H. pylori* infection in an accurate and quick way an which avoided the occurrence of false positive results.
The solution to this problem was not obvious. The concept developed by the present invention was indeed different from the disclosure of document (5), and is represented by the use of uncoated tablets wherein the components and the disintegration time had to be adapted by the hardness of the tablet. The disintegration time had to be not too short, since otherwise the contamination with urea producing bacteria in the oral cavity occurs, and consequently false positive deduction results could be produced. On the other hand, the disintegration time had also to be not too long, otherwise a detection within a reasonable time period after administration is not possible. It had thus to be a compromise between a short and a long disintegration time. This was confirmed by the teaching of document (18) which indicated that the disintegration time had to be adapted to be comprised between 2 and 5 minutes.
The concept of the present invention was different, since the presence of a coating rendered unnecessary to control the disintegration time of the core composition and thus the hardness of the tablet. The protection against bacteria of the oral cavity was provided by the coating. This coating enabled the skilled person to use core excipients that resulted in a fast disintegration of the core. This concept could not be deducted from the prior art.
As regards the coating, document (5) did not give any information regarding the amount and type of coating which could be used, so that the choice of specific

coating with hydroxypropylmethyl cellulose could not be deducted from this document. There was no further pointer in document (7) that the use of the coating of claim 1 of the main request in a specific amount was suitable for obtaining the result in minimization of the risk of false positive results at the urease breath test.

As regards inventive step in relation with auxiliary request 1, there was a further advantage over document (5). It was shown in the Table 3 of the patent that the disintegration time of the core was less than one minute or lower. The tablets of document (5) had a disintegration time of 1 to 5 minutes, as confirmed by document (18).
The tablets of the present invention thus provided a shorter disintegration time in comparison to the uncoated tablets of document (5). This had an effect on the minimization of the risk of false negative results, when the tablet disintegrated only on the intestinal level and not in the stomach level, as in the invention. The coating thus avoided false positive results and the core composition avoided the risk of false negative results.
The problem to be solved was the provision of a composition for diagnosing *H. Pylori* improved in that the risk of false negative and false positive results was diminushed. Document (5) did not provide compositions which could minimize the risks of false positive and false negatives simultaneously and there was no evidence that such tablets avoided this risk.

The arguments were the same for the other auxiliary requests.

XIII. Requests

The appellant (opponent) requested that the decision under appeal be set aside and that the European patent be revoked.

The respondent (patent proprietor) requested that the decision under appeal be set aside and the patent maintained in accordance with the claims of the Main Request or of Auxiliary Requests 1, 2, 3 or 4, all filed at the oral proceedings.

Reasons for the Decision

1. Admission of the requests into the proceedings

The main request and auxiliary requests 1-4 correspond to auxiliary requests 3 and 5-8 filed in response to the statement of grounds of appeal, thus at the earliest stage of the appeal proceedings and their admission into the proceedings was not contested by the appellant. The Board thus sees no reason not to admit them into the proceedings (Article 13 RPBA).

2. Main request - Inventive step

2.1 The invention relates to an oral formulation for a urea breath test, with which an *H. pylori* infection of the gastric mucosa can be detected and diagnosed expediently and non-invasively by the urea breath test and which is free from the risk of a false positive test because of complete elimination of the influence of urease-producing bacteria inhabiting the oral cavity, throat and other tissues excepting the gastrointestinal tract. A further object of the present invention is to provide a pharmaceutical preparation

with which the presence of *H. pylori* can be detected quickly without a time lag (see par. [0008], [0009] and [0010] of the specification). The pharmaceutical formulation of the invention thus shows an in vivo behavior such that it remains undissolved in the oral cavity but, upon entry into the stomach and dissolves quickly to allow the labelled urea to disperse rapidly throughout the stomach.

2.2 The respondent considered document (5) as closest state of the art.

Document (5) relates to a tablet containing isotope-labeled urea, an inorganic compound, an organic compound and a disintegrant for diagnosing the infection with urease-generating bacteria, particularly *Helicobacter pylori* (see page 2, lines 5-6 and 30-31). The disintegration time of the tablet in stomach is 5 seconds to 10 minutes, preferably 10 seconds to 2 minutes and can be adjusted either according to the hardness or on the amount of the disintegrant to be added (see page 3, lines 9-16). As regards the harness of the tablet, if the disintegration time of the tablet is 60 seconds, the tablet has a hardness of preferably 5 kgf or more, preferably 8 kgf or more. If the disintegration time of the tablet is 30 seconds, the tablet is of hardness of preferably 3 kgf or more, preferably 6 kgf or more (see page 3, lines 34-41).

The tablets disclosed in document (5) may be coated with various coatings, such as sugar coatings (see page 4, line 6).

Example 4 shows a tablet comprising as excipients cellulose, corn starch, polyplasdone and hydroxypropyl

cellulose, while example 5 shows a tablet comprising lactose, cellulose and hydroxypropyl cellulose, and example 6 a tablet with corn starch, polyplasdon, and hydroxypropyl cellulose. All the tablets disclosed in these examples comprised also magnesium stearate.

Test example 4 of document (5) shows a tablet comprising ^{13}C-urea, cellulose, mannitol and polyplasdone (see page 6) which is administered to subjects infected and non-infected with *Helicobacter pylori*, in comparison with a an aqueous solution comprising also ^{13}C-urea. Table 5 presents the content of $^{13}CO_2$ expressed in ‰ in the whole carbon dioxide expired air. This test example shows that the influences of oral bacterial flora on the tablet of ^{13}CO2-urea was suppressed so that rapid and accurate diagnosis of the infection can be practiced, thus explicitly the absence of false positive results (see page 6).

Document (5) thus does not show directly and unambiguously the specific combination of excipients of the core composition claimed in the main request, namely at least one member of the specific saccharides, celluloses and starches, with the presence of a coating comprising a specific water-soluble polymer around the tablet.

3. According to the respondent, the problem was seen as the provision of a preparation minimizing the risk of false-positive results while still obtaining a suitable response within the appropriate time limit, and simultaneously allowing a greater freedom with regard to the choice of excipients.

4. As a solution to this alleged problem, claim 1 of the main request proposes a preparation which is in particular coated with a coating agent comprising a water-soluble polymer, which is at least one member of the group consisting of pullulan, dextrin, alkali metal alginate, hydroxypropylcellulose, hydroxypropylmethylcellulose, methylcellulose and polyvinylpyrrolidone and wherein in particular the excipient component of the core composition comprises at least one member selected from the group consisting of lactose, sucrose and glucose, at least one member selected from the group consisting of crystalline cellulose,—carboxymethylcellulose calcium and croscarmellose sodium, and at least one member selected from the group consisting of starch, carboxymethylstarch sodium, hydroxypropylstarch, and partially pregelatinized starch.

4.1 It has to be investigated whether there is sufficient evidence supporting the alleged effect.

4.1.1 The patent in suit provides in example 3 and corresponding figure 1 an experiment to evaluate the effects of the tablets of example 1 comprising ^{13}C-urea, lactose, crystalline cellulose, corn starch coated with a coating comprising hydroxypropylmethyl cellulose on *H. pylori*-positive subjects and *H. pylori*-negative subjects with or without a mouth-washing step.
It is apparent from Fig. 1 that when the coated preparation of the present invention was used as a test reagent in *H. pylori*-negative subjects, omission of mouth washing did not introduce a change or only a little change in the difference between the ^{13}C value of exhaled air before and after tablet intake, namely the Δ^{13}c value expressed in ‰, that might be attributed to the influence of mouth and throat bacteria (see Figure

1 and par. [0061]-[0062]), whereas the $\Delta^{13}c$ value reflecting the urease activity of *H. pylori* in the stomach could be detected in *H. pylori*-positive subjects. Figure 1 shows thus that there were no false positive results in *H. pylori* negative subjects, whether or not a mouth-washing step was performed.

This experiment of example 3 and figure 1 does not, however, constitute evidence to support the assertion that the risk of false positives is minimized in comparison to the uncoated preparations of document (5). Said experiment does not present a direct comparison with uncoated preparations, but only allows an indirect comparison with the results of the experiments performed in document (5). The results expressed in example 3 and figure 1 of the contested patent indeed relate to the $\Delta^{13}c$ value expressed in ‰, which is the the difference between the ^{13}C value of exhaled air before and after tablet intake, whereas the Test example 4 and Table 5 of document (5) express the experimental results directly as the content of $^{13}CO_2$ (expressed in ‰) in the whole carbon dioxide expired air after tablet intake.

As regards the test example 4 and Table 5 of document (5), they show unequivocally that the tablets disclosed in document (5) do not release urea in the mouth or the throat, but only later on the stomach level. Evidence of the contrary has not been provided by the appellant.

It is thus not possible to conclude from these experiments that either the coated form or uncoated form provides a better result. The contested patent thus does not provide any evidence that the technical problem regarding the minimization of the risk of false positive results has been solved.

4.1.2 Document (12) has been further submitted by the respondent. This document repeats a disintegration/ dissolution test comparing the preparations according to the invention with those of example 7 of document (5). It shows that uncoated preparations according to example 7 of document (5) start to erode after a couple of seconds in water in comparison to the coated preparations according to the invention for which no erosion can be seen after 5 seconds.

An equivalent experiment is described in Table 3 of the contested patent, wherein the disintegration time of a given tablet was measured in the absence of any coating and in the presence of an increasing amount of coating relative to the weight of the core composition. This test demonstrates that said uncoated tablet has a quicker disintegration time in water, and that the coating provided a slight release retardation (see par. [0055]). According to Table 3, the disintegration time of said coated tablets according to the invention ranges from 5 seconds to 55 seconds (see Table 3).

The tests performed in document (12) and in Table 3 of the contested patent are however completely silent on the hardness of the compressed tablet and the variable amount of disintegrating agent. In document (5), the tablets of example 7 are for instance compressed at variable hardnesses ranging from 7.1 kgf to 10.2 kgf, and the disintegration time of the corresponding tablets ranges from 33 seconds to 88 seconds, a disintegration time which fits with the results obtained in Table 3 of the contested patent. Document (12) does not present a comparison with uncoated tablets with such different hardness levels. Yet the tablet hardness is presented as one of the essential

parameters to modulate the disintegration time in document (5).

The tests performed in document (12) thus do not enable convincing conclusions to be drawn as to an effect of the compositions according to the invention in comparison with compositions according to document (5), as regards a possible quicker dissolution of uncoated tablets in the mouth or in the throat involving a higher risk of false positive results at the urea breath test. These tests are indeed not sufficient to invalidate the results presented in Test example 4 and Table 5 of document (5).

4.1.3 Documents (10) and (11) were submitted during the opposition proceedings and document (15) was submitted during the appeal proceedings

Document (10) provides a comparison of the disintegration time, hardness and friability between an uncoated tablet comprising lactose, cellulose and starch and uncoated tablets comprising only one or two of the same excipients. The uncoated tablet comprising lactose, cellulose and starch achieves a shorter disintegration time, namely in the range of 25-35", as well as a quicker urea dissolution than the comparative tablets. The other tablets achieve a disintegration time of at least 2'30".

Document (11) provides a comparison of the disintegration time between a uncoated tablet according to example 1 of the patent comprising lactose, cellulose and starch to comparative tablets A and B, comprising respectively lactose, hydroxypropyl cellulose and starch for the tablet A, and lactose with sodium croscarmellose for the tablet B. The tablet

according to example 1 has a disintegration time 25-45", while tablets A and B achieve respectively a disintegration time of 3'55"-6'25" and 35"-45".

Document (15) measures the lag time and the disintegration time of various tablets made from a core composition comprising lactose, cellulose, and starch and a coating made from HPMC, PEG, titanium dioxide and talc. It shows a lag time ranging from about 10-15 seconds to 25-35 seconds is achieved, depending on the amount of the coating composition relative to the weight of the total composition, and a disintegration time ranging from 10-15 seconds to 40-60 seconds. A comparative example without starch in the core composition achieved a disintegration time of 3 minutes 40 seconds to 4 minutes 20 seconds after a lag time of 25-30 seconds.

Documents (10), (11) and (15) thus show the great freedom with regard to the choice of excipients that the claimed subject-matter affords. However, these documents not only do no provide any evidence as to the existence of an effect over the tablets disclosed in document (5) but highlight their similarities. Document (5) shows tablets comprising excipients such as mannitol, lactose, cellulose, croscarmellose sodium, carboxymethylcellulose calcium, starch, hydroxypropyl starch, or equivalents thereof having similar properties as filling agent, binding agents or disintegrating agents, which is nothing more than the respective function of lactose, cellulose and starch (see document (5), page 2, lines 57-58, page 3, lines 17-33; all examples). Said tablets achieve a disintegration time which can be modulated through the amount of disintegrating agent and the tablet hardness. A tablet disintegration time ranging between 22 seconds

and up to 679 seconds, with a majority of cases comprised between 30 seconds and 180 seconds can thus be achieved by this tailoring method (see document (5), Tables 4, 6, 7). All these tablets are made with different excipients which are interchangeable given their properties, allowing also a great freedom with regard to the choice of excipients.

The claimed invention does not present any advantage over the teaching of document (5) as regards the obtention of a preparation obtaining a suitable response within the appropriate time limit and allowing a greater freedom with regard to the choice of excipients.

4.1.4 According to established case law of the boards of appeal, alleged advantages to which the patent proprietor merely refers, without offering sufficient evidence to support the comparison with the closest prior art, cannot be taken into consideration in determining the problem underlying the invention and therefore in assessing inventive step (Case Law of the Boards of Appeal, 7th edition, 2013, I.D.4.2.)

In the absence of experimental or technical evidence or arguments establishing a minimum plausibility, it is not possible to acknowledge the existence of an improvement over the prior art. The technical problem must therefore be reformulated as the provision of an alternative preparation for the diagnosis of Helicobacter pylori, namely an alternative preparation capable of minimizing the risk of false positive results while still obtaining a suitable response within the appropriate time limit and allowing a greater freedom with regard to the choice of excipients.

In view of the information found in the examples of the contested patent, the board is convinced that the problem has been plausibly solved (see points 4.1.1-4.1.3 above).

4.2 It remains to determine whether the solution was obvious to the person skilled in the art.

Document (5) envisages as main excipient for the tablet either mannitol, lactose or cellulose (see page 2, lines 57-58), in combination with usual excipients such as disintegrating agents or binding agents. According to the disclosure of document (5), any disintegrant for use in formulation may be used, inter alia crosscarmellose sodium, carboxymethyl cellulose and the calcium salt thereof, hydroxypropyl starch and the like(see page 3, lines 9-19). Additionally, the tablet may contain other additives frequently used for the formulation of other tablets, such as sweetening agents or binders. Examples of the sweetening agents include inter alia sucrose, and examples of the binders include inter alia starch and purified sugar (see page 3).
Test example 4 of document (5) shows a tablet comprising ^{13}C-urea, cellulose, mannitol and polyplasdone (see page 6), while example 4 shows a tablet comprising cellulose, corn starch, polyplasdone and hydroxypropyl cellulose, example 5 shows a tablet comprising lactose, cellulose and hydroxypropyl cellulose, and example 6 a tablet with corn starch, polyplasdone, and hydroxypropyl cellulose.
It follows that all compounds of the excipient component claimed in claim 1 of the main request are known and identified in document (5).

The constitution of the excipient component of claim 1 of the main request turns out to be merely the result of arbitrary choices among known alternatives and lying within the routine activity of the skilled person.

As regards the coating, document (5) suggest the use of a coating, by stating that "the resulting tablet may be coated with various coatings and sugar coatings, if necessary" (see page 4). Coatings comprising hydroxypropylmethyl cellulose are common film-forming coatings as shown by the common general knowledge document (7). Said document (7) gives the reasons to coat tablets, namely inter alia for protection against moisture, or providing controlled (see pages 669-679, "Reasons for coating tablets"). As film-coating solutions, this document mentions inter alia the use of hydroxypropylmethyl cellulose in combination with a plasticizer, such as PEG, and colorants.

The solution of claim 1 of the main request is therefore known from document (5) in combination with the common general knowledge of the skilled person.

4.3 Further arguments from the respondent

According to the respondent, the concept of the claimed invention was totally different from the concept disclosed in document (5). The claimed invention comprises a core with a coating aiming to protect the core from contact with bacteria in the oral cavity. Thanks to the coating it was not necessary to adapt the hardness of the tablet core tablet.
In document (5), the hardness had to be adapted to provide a disintegration time which was a compromise between a too short and a too long disintegration time. The disintegration time had to be ideally comprised

between 2 and 5 minutes, as confirmed by document (18) (see document (18), page 317, first par. "Discussion"). The present invention does not need to find such a compromise, since the coating provided a lag time which was sufficient to the quick disintegrating core composition to rapidly release urea in the stomach.

The Board could not follow this argument. It is not contested that the teaching of document (5) shows that a compromise in the tablet hardness must be found in order to achieve a disintegration within the stomach. It is however not correct to argue that the claimed core composition provides inevitably a quick release of urea when the coating has dissolved. Claim 1 of the main request does not comprise any restriction or specification regarding a quick release or disintegration time of the core composition, and the claimed excipients and also their claimed quantities are such that the claimed core composition comprises without any doubt quick release formulation, but also compositions disintegrating within 2 to 5 minutes with the stomach, such as the compositions disclosed in document (5). In fact, the compositions claimed by claim 1 of the main request encompasses also tablets having the disintegration profile of the tablets of document (5) with a supplementary coating.
The argument of the respondent thus cannot stand.

4.4 The subject-matter of claim 1 of the main request is not inventive and this request does not meet the requirements of Article 56 EPC.

5. Auxiliary request 1 - Inventive step

5.1 This request differs from the main request by the specification of the excipient component, namely a

combination of lactose, crystalline cellulose and starch and of the coating composition, namely hydroxypropylmethyl cellulose, PEG, titanium oxide and talc.

5.2 According to the respondent, this specific feature has a supplementary effect, namely the minimization of potential false negatives. This effect is linked with the shorter disintegration time of the coated preparation of the invention in comparison with the longer disintegration time of the tablets described in document (5). According to document (18), the disintegration time of the tablets of document (5) ranges from 2 to 5 minutes, which might release urea only on the intestinal level, thus producing false negative results (see document (18), page 317, first par. "Discussion").
On the other hand, the tablet of the present invention presents a disintegration which is much shorter, namely around one minute. Example 2 and Table 3 of the contested patent show indeed that such compositions have lag time ranging from 5 seconds to 20-40 seconds with a disintegration time of the core ranging between 10-15 seconds 45-55 seconds. This amounts to a total delivery time each limited to less than 1 minute. This result is confirmed directly by the tests (15) and indirectly by (10) and (11).

However, as argued previously for the main request, the Board cannot identify any difference between the release time of the tablet of the claimed invention and the tablet disclosed in document (5). Document (5) shows numerous compositions dissolving in around 30 seconds to 90 seconds, as for instance in Table 4, a disintegration time identical to the disintegration

shown in Table 3 of the contested patent or in document (15).

Consequently, there is no evidence or credible technical argumentation supporting the alleged effect, and as for the main request the technical problem is the provision of an alternative of an alternative preparation for the diagnosis of *Helicobacter pylori*, namely an alternative preparation capable of minimizing the risk of false positive or false negative while still obtaining a suitable response within the appropriate time limit, and allowing a greater freedom with regard to the choice of excipients.

5.3 The constitution of the excipient component or of the coating composition of claim 1 of the main request, namely a specific combination of lactose, crystalline cellulose and starch as regards the excipients component and of hydroxypropyl methyl cellulose, PEG, titanium oxide and talc, turns out to be merely the result of arbitrary choices among alternatives known from documents (5) or (7) and lying within the routine activity of the skilled person (see point 4.2 above).

5.4 Consequently, the further restriction in claim 1 of auxiliary request 1 has no incidence on the reasoning and conclusions on inventive step raised above for the main request.

The subject-matter of claim 1 of auxiliary request 1 is not inventive and this request does not meet the requirements of Article 56 EPC.

6. Auxiliary request 2 - Inventive step

The subject-matter of claim 1 of auxiliary request 2 differs from the subject-matter of claim 1 of auxiliary request 1 by the specification of the amount of coating agent of 0.5-3 parts by weight of the core composition.

This amendment has no incidence of the formulation of the problem, since no effect was related thereto.

As to the obviousness, document (7) mentions that the usual weight increase of a tablet due to the use of a film-coating composition is 2-3% (see Table 40.1, page 673). The amount claimed in claim 1 of auxiliary request 2 is therefore an arbitrary measure within the ordinary routine of a skilled practitioner and cannot contribute to an inventive step.

Hence, the amendment does not have any incidence on the reasoning and conclusions on inventive step outlined for the main request and auxiliary request 1, which apply *mutatis mutandis* to claim 1 of auxiliary request 2. No inventive step can therefore be seen as a result of the specification of the amounts of coating agent.

Auxiliary request 2 does not meet the requirements of Article 56 EPC.

7. Auxiliary request 3 - Inventive step

The subject-matter of claim 1 of auxiliary request 3 differs form the subject-matter of claim 1 of auxiliary request 1 by the further restriction regarding the amounts of the compounds of the core composition, namely in that the core composition comprises:
"30-70 weight% of isotope carbon-labeled urea,
35-65 by weight% of an excipient component and,
0.1-0.7 weight% of a lubricant component".

This restriction corresponds to the amounts disclosed in at least examples 4-6 of document (5) and is not linked with any specific effect or improvement, and thus has no incidence on inventive step.

Consequently, auxiliary request 3 does not meet the requirements of Article 56 EPC.

8. Auxiliary request 4 - Inventive step

The subject-matter of claim 1 of auxiliary request 4 differs from the subject-matter of claim 1 of auxiliary request 1 by the specification of the excipients and their amounts, namely:
(i) a core composition comprising:
50 weight% of ^{13}C-labeled urea,
17.2 weight% of lactose
30.0 weight% of crystalline cellulose
2.5 weight% of corn starch and
0.3 weight% of magnesium stearate;
and
(ii) a coating agent **consisting of 60 weight% of hydroxypropyl methylcellulose, 20 weight% of polyethylene glycol, 10 weight% of titanium oxide and 10 weight% of tal,**
wherein the coating agent is present in an amount of **2 parts by weight** based on 100 parts by weight of the core composition."

An effect linked with these restrictions has not be shown and is thus not credibly demonstrated. As for the main request the technical problem must be reformulated as the provision of alternative compositions.

All excipients were known from documents (5) or (7), and the selection of specific claimed amounts appears to represent an arbitrary measure within the ordinary routine of a skilled practitioner and cannot contribute to an inventive step.

Consequently, auxiliary request 3 does not meet the requirements of Article 56 EPC.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The patent is revoked.

The Registrar: The Chairman:

S. Fabiani J. Riolo

Decision electronically authenticated