LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Espikur
(^{13}C-urea)

SE/H/1829/01/DC

This module reflects the scientific discussion for the approval of Espikur. The procedure was finalised on 2019-04-30. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

Laboratoires Mayoly Spindler has applied for a marketing authorisation for Espikur, 50 mg, tablet. The active substance is ^{13}C-urea (after oral ingestion, labelled urea tablet reaches the stomach, where it disintegrates rapidly. In the case of infection with *Helicobacter pylori*, ^{13}C-urea is metabolised by the enzyme urease of *Helicobacter pylori)*.

For approved indications, see the Summary of Product Characteristics.

The marketing authorisation has been granted pursuant to Article 8(3) of Directive 2001/83/EC.

For recommendations to the marketing authorisation not falling under Article 21a/22 of Directive 2001/83/EC and conditions to the marketing authorisation pursuant to Article 21a or 22 of Directive 2001/83/EC to the marketing authorisation, please see section VI.

II. QUALITY ASPECTS

II.1 Drug Substance

The structure of the drug substance has been adequately proven and its physico-chemical properties are sufficiently described.

The manufacture of the drug substance has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

The drug substance specification includes relevant tests and the limits for impurities and degradation products have been justified. The analytical methods applied are suitably described and validated.

Stability studies confirm the retest period.

II.2 Medicinal Product

The medicinal product is formulated using excipients listed in section 6.1 in the Summary of Product Characteristics.

The manufacturing process has been sufficiently described and critical steps identified.

The tests and limits in the specification are considered appropriate to control the quality of the finished product in relation to its intended purpose.

Stability studies have been performed and data presented support the shelf life and special precautions for storage claimed in the Summary of Product Characteristics, sections 6.3 and 6.4.

III. NON-CLINICAL ASPECTS

III.1 Introduction

No new animal or in vitro studies have been performed with Espikur (^{13}C-urea). This is acceptable since the use of ^{13}C-urea is well established in the clinic. The submitted non-clinical overview on the pre-clinical pharmacology, pharmacokinetics and toxicology is considered to be adequate

III.2 Ecotoxicity/environmental risk assessment

Urea is an endogenous product of protein and amino acid catabolism in mammals.
The active substance of Espikur (^{13}C-urea) is thus a natural substance, the use of which will not alter the concentration or distribution of the substance in the environment. Therefore, ^{13}C-urea is not expected to pose a risk to the environment.

IV. CLINICAL ASPECTS

IV.1 Introduction

Helicobacter pylori (HP) is a gram-negative bacterium colonizing the gastro-intestinal (GI) tract causing local inflammation in the stomach and duodenum (Brown, 2000). HP infection of the GI tract has been shown to be a major contributor to diseases including peptic ulcer disease, MALToma lymphoma and gastric cancer (Watari *et al*, 2014). Reliable methods for detection of HP infection are a major clinical necessity.

Previously, biopsy-based tests represented the clear “gold standard” to diagnose HP infection. However, currently UBTs, using either ^{13}C- or ^{14}C-urea, are reliable with regard to sensitivity and specificity (Braden *et al*, 2007; Garza-González *et al*, 2014; Dill *et al*, 1990; Moayyedi *et al*, 1999). The UBTs have the advantage of identifying only current infection, so can be used both to identify primary infection and to monitor the efficacy of the treatment of the eradication of HP infection. UBT tests have further advantages compared to biopsy: they are non-invasive, easy to perform and sample the entire stomach.

According to the latest Maastricht V guidelines (Malfertheiner *et al*, 2017) for the management of HP infection, UBT is the most investigated and best recommended non-invasive test in the context of a ‘test-and-treat strategy’. The ^{13}C-UBT is the best approach to the diagnosis of HP infection, with high sensitivity and specificity, excellent performance and ease of use (Gisbert and Pajares, 2004; Nocon *et al*, 2009). Out of 12 RCTs comparing the 'test-and-treat' strategy to oesophago-gastro-duodenoscopy or PPI therapy, eight (66%) were performed with UBT, four (33%) with serology, and none with SAT.

IV.2 Pharmacokinetics and Pharmacodynamics

Espikur tablet is used for diagnosis of HP infection. This is governed by the ^{13}C-urea in Espikur being enzymatically hydrolysed by bacterial urease (produced exclusively by HP) to 13CO2 in the gastrointestinal tract after administration (see below).

$H_2N(^{13}CO)NH_2 + H_2O \rightarrow 2NH_3 + {}^{13}CO_2$

The 13CO2 diffuses into the blood vessels and from there it is transported as bicarbonate into the lungs and liberated as 13CO2 with exhaled air.

Subsequently, presence/absence of HP can thus be determined by measuring a change in the 13C/12C isotope quota in exhaled air.

No specific pharmacodynamic or pharmacokinetic studies have been conducted on the Urea Breath Test of 50 mg ^{13}C-urea which is acceptable. A single oral dose of 50 mg ^{13}C-urea can be considered as negligible in relation to the daily endogenous urea turnover.

IV.3 Clinical efficacy

Espikur is the same product that is previously authorized under the name Diabact UBT.

Five clinical trials on Diabact® UBT tablet, which are part of the clinical development programme of the product, were considered for the present application.

One Phase II (DYS 01B), 3 Phase III (DB 01A, DB 004, and DB 007), and 1 Phase IV (DB 008) clinical trials were conducted.

In addition, three published studies (Wong *et al*,2003; Hamlet *et al*,1999 and Gatta *et al*, 2003) were considered relevant.

One additional published study (Porter *et al*, 2009;) were also considered as additional in supporting the product performance.

Study design and objectives
Aim of the trials in the development programme was to determine the clinical usefulness of Diabact® UBT and, therefore, it assessed the different aspects of product performance.

Table 1 Clinical trials supporting the different aspects of Diabact® UBT activity

Study	Diabact® activity	Objective	No. of patients
DB 004	**Test performance**	Comparison to SoT and UBT water solution diagnostic (ESP,-European Standard Performance)	149
DB 01A	**Test performance**	Comparison to SoT and UBT water solution diagnostic (ESP)	40
DYS 01B	**Cut-off optimization**	Optimisation of cut-off value for HP status determination	170
DB 007	**Cut-off optimization**	Optimisation of cut-off value for HP status determination	885
DB 008	**Dose bridge (100 mg → 50 mg)**	Comparison between clinical trials' dose (100 mg) and marketed dose (50 mg)	150

Wong *et al* (2003)	**Performance (incl. post-eradication pts)** **Cut-off**	Comparison to gold standard (rapid urease test and histology) of 50 mg dose	200
Hamlet *et al* (1999)	**Performance**	Comparison to gold standard (UBT, culture, histology and CLO test)	667
Gatta *et al* (2003)	**Performance (pre and post eradication pts)**	Comparison with endoscopy gold standard and conventional water solution C^{13} UBT	113

Studies and DB 004 and DB 01A – with DB 004 being pivotal (clear product performance in a rather large study) – support the performance of Diabact® UBT in detecting HP infection in comparison to SoT and UBT water solution diagnostic. Even though the current "gold standard" used for HP infection diagnosis are UBTs, these studies clearly show the performance of Diabact® UBT also compared to older methods.

In studies DYS 01B and DB 007, the cut-off for diagnosis is optimised using statistical methods. Thus, these studies are relying on that Diabact® UBT performance in diagnosing HP infection has been shown in other studies (DB 01A and DB 004).

Lastly, study DB 008 supports the use of a lower dose, 50 mg, as compared to the higher dose used in all other studies. The 50 mg dose is in line with the one approved and marketed.

The three published studies on Diabact® UBT Wong *et al* (2003), Hamlet *et al* (1999) and Gatta *et al* (2003) have also been included in this application. These studies provide a general support to Diabact® UBT performance for diagnosis of HP infection (both in untreated and treated patients, for Wong *et al* 2003). As gold standard diagnostic reference and histology were used as comparator, these studies support the internal studies DB 01A and DB 004 which bridge the performance of Diabact® UBT against SoT diagnostic markers.

The Hamlet study also dealt with the “diagnostic validity” of the test, i.e. to ascertain its clinical usefulness in assessing both HP status and the efficacy of an eradication therapy.

The endpoints chosen to compare the ^{13}C UBT with the SoT/gold standard (sensitivity and specificity) are in line with the requirements of CHMP “Guideline on Clinical Evaluation of Diagnostic Agents (CHMP, 2009)”, which states: “*For most diagnostic agents, appropriate co-primary endpoints are sensitivity and specificity of an investigational agent*”.

The primary variable in all studies was the excess δ-$^{13}CO_2$ excretion (per mil), in expired breath measured by IRMS.

Trial populations

The overall populations enrolled in the 5 clinical trials include 1419 patients, 1394 of whom having received at least one 50 mg or 100 mg dose of Diabact® UBT.

Additional 980/1076 (treated/enrolled) patients were analysed in the studies by Wong *et al* (2003), Hamlet *et al* (1999) and Gatta *et al* (2003) for a total of 2374 treated subjects.

All patients included in the study analyses were tested for HP status due to dyspepsia/GI complaints of various aetiology (oesophagitis, gastro-oesophageal reflux, gastric or duodenal ulcer, non-ulcer dyspepsia, functional dyspepsia) or were followed-up for HP eradication and/or ulcer healing (study by Wong *et al*, 2003). In the study by Hamlet *et al* (1999) 147 healthy volunteers were also tested.

Adult and elderly patients (18 to 88 years) of both sexes were studied in the prospective studies. According to SmPC, the use of Espikur is not recommended in children due to the lack of data in this population.

Male and female patients were equally well represented in the overall population of the studies. No relevant differences were observed across studies as for demographic and baseline characteristics of the patients.

Common exclusion criteria included pregnant or lactating women, previous treatment with anti-secretory/prokinetic/antacid or antibiotic therapy during 2-4 weeks prior to the study drug administration, history of severe allergic disease, or presence significant diseases or conditions (like alcoholism or drug abuse) that may compromise the test results. Additional exclusion criteria were: history of oesophageal or GI surgery or any other abdominal surgery except appendectomy (DYS 01B), gastric surgery or earlier treatment for HP infection (DB 004; DB 008; Wong *et al* 2003; Hamlet *et al,1999*).

The population involved constitutes a representative sample of the population consulting physicians with GI complaints and which has a significant impact on the resource use of any national Health System, and it thus reflects the patient group in which the diagnostic agent is intended to be used, in line with the requirements of the relevant diagnostic agent guideline (CHMP, 2009).

In this regard, the fact that all patients – excluding the group of healthy volunteers in the Hamlet study – was affected by dyspepsia is very important, especially in view of the "Test and Treat" approach proposed by the Maastricht V/ Florence Consensus Report (Malfertheiner *et al*, 2017).

The characteristics of this population, which mostly include adult or elderly dyspeptic patients, are considered representative for the population of HP infected patients for whom the use of ^{13}C-urea 50 mg tablets would be indicated in the clinical practice.

Statistical considerations

The sample size of the trials included in the development programme clinical trials ranged from 40 to 170 subjects (mean, 102), except for the Phase IV study (DB 008) which retrospectively analysed 885 patients.

As for the published studies by Wong *et al* (2003), Hamlet *et al* (1999) and Gatta *et al* (2003), the sample size was 200, 667 and 113 subjects, respectively.

The statistical analyses are used in comparative trials to establish equivalence or non-inferiority between Diabact® UBT and the reference UBTs. Analysis of variance (Study DB 01A, Hamlet study), McNemar's test (Studies DB 004 and 008), Student's t-test, the chi-

square test and Fisher's exact test (Wong study) were employed; in all cases, 95% confidence intervals were computed, according to guideline recommendations.

In addition, a statistical simulation study was designed to perform indirect comparison between SoT (Histology, rapid urease test, serology and Hp Plus UBT) and the registered dose Diabact UBT.

IV.4 Clinical safety

The endogenous nature of urea supports the safety of ^{13}C-urea 50 mg tablets.

Urea is a physiological substance produced by the human organism. The human body forms an average of 25 to 30 grams of urea daily – more than this in persons on high-protein diet and less in persons on low-protein diet. All this urea is excreted in the urine, keeping the plasma urea concentration at approximately 26 mg/100 mL (Martindale, 2017). ^{13}C is a naturally occurring, non-radioactive, stable isotope of carbon. 97% of ingested ^{13}C-urea will be eliminated by breath and urine within 3 days.

A single oral dose of 50 mg ^{l3}C-urea is considered negligible (<2%) in relation to the daily endogenous urea turnover. Assuming the presence of *Helicobacter pylori* in the stomach, part of the urea is cleaved into carbon dioxide and ammonia. The carbon is rapidly absorbed locally and distributed. The ammonia formed id absorbed and completely metabolized by the liver, via amino acids, to form urea. Any urea passing through the stomach will be absorbed and enter the physiological pool where it will be distributed into extracellular and intracellular fluids, and subsequently excreted via the kidneys. (EMA, 2005). Moreover, the intrinsic toxicity of urea, and therefore of ^{13}C-urea (which is non-radioactive and has the same physicochemical behaviour), is very low.

When used clinically as a diuretic or as an agent to reduce intracranial and intraocular pressure, in fact, it is administered, both orally and IV, at daily doses between 20 and 100 g. It is therefore extremely unlikely that the administration of a single dose over 400 times lower than the lowest pharmacological dose could cause any effect in the organism.

In the absence of bacterial urease the administered urea, after being absorbed by the GI tract, is metabolized like endogenous urea, without causing any safety concern (Martindale, 2017), ^{13}C is a natural, stable and non-radioactive isotope, which has no known pharmacodynamic effects. The total daily intake of ^{13}C-isotope in food is in average 2.7 g.

Clinical Trial Data

The development programme data include 5 clinical trials on ^{13}C-urea 50 mg tablets and cover a total of about 1400 subjects who received at least one dose of Diabact® UBT.

In these studies, patients were exposed to one 100-mg oral dose of Diabact® UBT. In study DB 008, patients received two additional 50-mg doses of the product.

In the comparative studies (DB 01A and DB 004), the patients received an additional dose of the standard reference product (^{13}C-urea 100 mg water solution).

With the exception of retrospective Study DB 007, which also included paediatric patients (age range, 9-93 years), the population studied consisted of exclusively adult or elderly patients (age range, 18-88 years) with dyspepsia/GI complaints.

In all of these trials, the study population reflected the population targeted for Espikur use in the clinical practice in terms of both indication and age category. In fact, according to the ^{13}C-urea 50 mg tablets SmPC, the product is indicated for HP diagnosis and must not be used in patients younger than 18 years.

Safety was evaluated in all trials through the monitoring and assessment of AEs.

Only minor AEs were reported for ^{13}C-urea 50 mg tablets in the clinical studies, e.g. difficult to swallow (1 patient), stomach pain/upset (7), nausea/vomiting (1), sour taste (4), fatigue, dizziness, and vertigo (1 each).

All AEs were mild or moderate in severity and no serious AE was reported. None of the AEs was considered by study Investigators as related to study drug. The following adverse events are included in the SmPC 4.8:

Gastrointestinal disorders
Very rare: stomach pain

General disorders and administration site conditions
Very rare: fatigue

Nervous system disorders
Very rare: parosmia

Published Evidence

In the study by Hamlet *et al* (1999), the patients were exposed to one 100-mg oral dose of Diabact® UBT plus an additional dose of the standard reference product (^{13}C-urea 100 mg water solution). The population included over 650 adult subjects with dyspepsia.

In the comparative study by Wong *et al* (2003) on 200 adult Chinese dyspeptic subjects, patients received one 50-mg dose of Diabact® UBT. The 50-mg tablet-based 13C-UBT was performed after an overnight fast. After the collection of a baseline exhaled breath sample in a vacutainer, the 50-mg ^{13}C-urea tablet (Diabact® UBT) was swallowed with 200 mL of water. Further breath samples were taken at 10, 20 and 30 min. No test meal was used before the breath test. The sensitivities, specificities and accuracies of 13C-UBT were calculated at 10, 20 and 30 min.

In this case, too, the study population reflected the population targeted for Espikur use in the clinical practice in terms of both indication and age category.

No mention of AEs was made, either for the UBT or for the other more invasive tests.

Given the general considerations made, it is however safe to assume that very few, if none at all, adverse reactions imputable to the UBT occurred during the trials and that none of them were severe or serious.

Post-Marketing Data
Diabact® UBT has been approved in Sweden in 1999 and has been on the market since then. Since approval one adverse reaction (preferred term:Rash) has been reported. This report was a spontaneous consumer report considered non serious with a possible causal relationship to the product. No particular safety concerns have been discovered in the medical literature.

On the whole, neither particular issues nor safety concerns have been discovered from Post-Marketing Surveillance (PMS) information that may influence the information reported in the SmPC. No changes to reference safety information were thus performed.

Conclusions on Safety
The human body forms an average of 25 to 30 grams of urea daily. A single dose of 50 mg of ^{13}C-urea is therefore not expected to produce adverse effects. Very few adverse events were reported in clinical trials, literature as well as postmarketing since 18 years. In conclusion, there is no significant information of any particular safety concerns in relation to this diagnostic test.

IV.5 Risk Management Plans

Risk Management Plan
The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Espikur.

Safety specification

Table SVIII.1: Summary of safety concerns

Summary of safety concerns	
Important identified risks	False negative or false positive results
Important potential risks	None
Missing information	Use in children, patients with gastrectomy

Pharmacovigilance Plan
Routine pharmacovigilance is suggested and no additional pharmacovigilance activities are proposed by the applicant, which is endorsed.

Risk minimisation measures
Routine risk minimisation is suggested and no additional risk minimisation activities are proposed by the applicant, which is endorsed.

Summary of the RMP
The submitted Risk Management Plan, is considered acceptable.

An updated RMP should be submitted:
- At the request of the RMS;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk

profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time, but via different procedures.

V. USER CONSULTATION

The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The language used for the purpose of user testing the PIL was English.
The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Beneficial effects

^{13}C-urea 50 mg UBT tablets are used for diagnosis of HP infection. The ^{13}C-urea in UBT is enzymatically hydrolysed by bacterial urease (produced exclusively by HP) to ^{13}CO2 in the gastrointestinal tract after administration and measured in the exhaled air from the patients. Diabact® UBT, was first registered in Sweden in 1999 (International Birth Date [IBD]: October 22nd, 1999) by Orexo AB. Espikur is the same product that is previously authorized under the name Diabact UBT.

As a diagnostic agent, ^{13}C-urea 50 mg tablet is submitted to the CHMP "Guideline on Clinical Evaluation of Diagnostic Agents" (CHMP, 2009). Diabact® UBT was approved using the 1.5‰ cut-off, for non-inferiority in comparison to established already approved products (as well as vs reference diagnostic methods accepted as SoT).

The Espikur 50 mg tablets is used for diagnosis of HP infection and is administrated at a single or repeated occasions. It is only to be used at a limited number of occasions and is not to be used chronically. Consequently, the exposure of Espikur 50 mg tablets to the individual patient is considered very low over time.

Uncertainties of the beneficial effects

If the patient chews the tablet, the test must be performed again as the risk of false positive results increase. A new test may be performed the following day. Antibiotics and proton pump inhibitors treatment may lead to false negative results. Therefore, the test must not be used until after at least four weeks after systemic antibacterial therapy and at least two weeks after last dose of acid antisecretory agents. These considerations are labelled.

There are insufficient data to recommend the use of [^{13}C urea] in patients with partial gastrectomy and in patients younger than 18 years.

Unfavourable effects

Minor adverse events were reported for these tablets in the clinical studies, e.g. difficult to swallow, stomach pain, sour taste. Many of these adverse events were not considered related to the study drug.

Benefit/risk balance

The application is recommended for approval from a quality perspective.

There are no objections to approval of Espikur (^{13}C-urea) from a non-clinical and clinical point of view.

In conclusion, the benefit risk of this product Espikur (^{13}C-urea) 50 mg tablets is positive and the application is approved.

List of recommendations not falling under Article 21a/22 of Directive 2001/83/EC in case of a positive benefit risk assessment

N/A

List of conditions pursuant to Article 21a or 22 of Directive 2001/83/EC

N/A

VII. APPROVAL

The Decentralised procedure for Espikur, 50 mg, tablet was positively finalised on 2019-04-30.

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Public Assessment Report – Update

Procedure number*	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse

*Only procedure qualifier, chronological number and grouping qualifier (when applicable)

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