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What is This?
Treatment With Liraglutide—a Once-Daily GLP-1 Analog—Does Not Reduce the Bioavailability of Ethinyl Estradiol/Levonorgestrel Taken as an Oral Combination Contraceptive Drug

Lisbeth V. Jacobsen, MSc, Jan Vouis, MD Charlotte Hindsberger, MSc, PhD, and Milan Zdravkovic, MD, PhD, MSc, Pharm Med

Liraglutide is a once-daily human GLP-1 analog for treatment of type 2 diabetes. Like other GLP-1 analogs, liraglutide delays gastric emptying, which could potentially affect absorption of concomitantly administered oral drugs. This study investigated the effect of liraglutide on the pharmacokinetics of the components of an oral contraceptive (ethinyl estradiol/levonorgestrel). Postmenopausal healthy women (n = 21) were included. A single dose of this contraceptive was administered. Blood samples for ethinyl estradiol/levonorgestrel measurements were drawn until 74 hours post dosing of the contraceptive during liraglutide and placebo treatments. The 90% confidence interval (CI) of the ratio of the area under the curve (AUC) (1.06; 90% CI, 0.99-1.13) for ethinyl estradiol (during liraglutide and placebo) was within defined limits, demonstrating equivalence. The 90% CI for the ratio of AUC for levonorgestrel was not fully contained within the limits (1.18; 90% CI, 1.04-1.34) (levonorgestrel AUC was 18% greater with liraglutide vs placebo). However, equivalence was demonstrated for levonorgestrel AUC$_{max}$ (1.15; 90% CI, 1.06-1.24). Equivalence was not demonstrated for maximum concentration (C$_{max}$): values for ethinyl estradiol and levonorgestrel C$_{max}$ were 12% and 13% lower with liraglutide versus placebo, respectively. Both reached C$_{max}$ ~1.5 hours later with liraglutide. No clinically relevant reduction in bioavailability of ethinyl estradiol/levonorgestrel occurred.

Keywords: Liraglutide; oral contraceptives; drug interactions; pharmacokinetics

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Liraglutide is a human glucagon-like peptide (GLP-1) analog that has been approved by the European Medicines Agency (EMA) (Victoza summary of product characteristics$^1$) and the US Food and Drug Administration (FDA) (Victoza prescribing information$^2$), among others, for the treatment of type 2 diabetes. Liraglutide is a modified molecule of native human GLP-1, with a substitution of Lys34 with Arg34 and an attachment of a carbon-16 fatty acid chain to Lys26. It therefore retains a high sequence identity (97%) to native GLP-1$^3$ and likely contributes to the low percentage (<12%) of antibody formation reported in recent confirmatory clinical studies.$^4-9$

Delayed release from the injection site, albumin binding in the circulation, and resistance to dipeptidyl peptidase (DPP) degradation give liraglutide a prolonged pharmacokinetic action compared with native GLP-1.$^{10}$ Liraglutide reaches maximum concentration at 8 to 12 hours ($t_{max}$) and has an elimination half-life of approximately 13 hours and is therefore compatible with a once-daily dosing regimen.

The majority of oral contraceptives undergo hepatic metabolism by enzymes of cytochrome-P450 (CYP450). However, as liraglutide does not rely on
this metabolic pathway, it is unlikely to interfere with the metabolism of oral contraceptives by means of inhibiting or inducing CYP450 enzyme activity.

Like native GLP-1, liraglutide has the potential to slow the rate of gastric emptying, which has been hypothesized to contribute to the appetite-reducing effect and subsequent weight loss observed with liraglutide. Like native GLP-1, liraglutide has the potential to slow the rate of gastric emptying, which has been hypothesized to contribute to the appetite-reducing effect and subsequent weight loss observed with liraglutide. Measurements of plasma paracetamol concentration, up to 8 hours post meal, indicated a minor delay of gastric emptying with liraglutide 1.2 mg and 1.8 mg compared with placebo, particularly over the first hour following a meal.

Changes in the rate of gastric emptying may potentially affect absorption of concomitant orally administered drugs. Studies have thus been performed to assess whether the pharmacokinetic properties of oral drugs were affected by liraglutide. The coadministration of atorvastatin, griseofulvin, lisinopril, and digoxin with liraglutide resulted in a slight shift in their absorption with later $t_{\text{max}}$ but generally there was no or very little change in total bioavailability as observed by area under the curve (AUC). Thus, for these compounds, the delays were considered to have no clinical relevance, as only minor reductions in maximum concentration ($C_{\text{max}}$) and time to $C_{\text{max}}$ ($t_{\text{max}}$) were reported and were most likely attributable to a slight delay in postprandial gastric emptying.

Oral contraceptives are common pharmacological methods of birth control. Most oral combination contraceptives contain estrogen in the form of ethinyl estradiol. This component has been associated with adverse effects, and therefore formulations with low content of ethinyl estradiol have been developed to minimize these effects. Any interaction that could lower the exposure outside the window of efficacy could result in failure of the drug to provide contraception. Drug interactions with oral contraceptives are most likely attributable to an interaction with absorption, metabolism, or excretion of estrogens.

The objective of this study is to investigate the effect of liraglutide (if any) on the pharmacokinetics of the components of an oral contraceptive drug containing ethinyl estradiol 0.03 mg and levonorgestrel 0.15 mg.

**METHODS**

**Study Design and Population**

This was a single-center, randomized, double-blind, placebo-controlled, 2-period crossover study comparing the influence of liraglutide and placebo on the pharmacokinetics of ethinyl estradiol and levonorgestrel, given as an oral combination contraceptive drug, Neovletta (Bayer AB, Solna, Sweden).

The study was in accordance with the Declaration of Helsinki and Good Clinical Practices and followed the accepted rules for interaction studies according to the FDA Guidance for Industry and the EMA guideline.

A total of 21 adult women participated in and completed the study. Informed consent was obtained before any study-related activities commenced. Postmenopausal women who had undergone oophorectomy or had at least 1 year of amenorrhea were selected for the study with the aim of eliminating any hormonal fluctuations that might influence the interpretation of the pharmacokinetics of ethinyl estradiol or levonorgestrel. Other criteria included a body mass index (BMI) between 18 and 30 kg/m² and the investigator’s judgment that subjects were in good health based on the results of medical history and physical examination including 12-lead electrocardiogram (ECG), vital signs, and blood and urinary laboratory assessments. Subjects with history of clinically significant renal, hepatic, cardiovascular, pulmonary, gastrointestinal, metabolic, or neurological diseases or other major disorders were excluded from the study.

**Drug Administration and Sample Collection**

The absorption of ethinyl estradiol 0.03 mg/levonorgestrel 0.15 mg, given as 1 single dose of an orally administered combination contraceptive, was investigated with the highest available dose of liraglutide (1.8 mg) at steady state and with placebo.

Each subject received either liraglutide or placebo once daily for 3 weeks, in random order, before switching to the alternate treatment (placebo or liraglutide) for 3 weeks. In each crossover period, subjects took liraglutide 0.6 mg (or corresponding injection volume of placebo) for week 1, followed by liraglutide 1.2 mg (or corresponding placebo) during week 2, and finally liraglutide 1.8 mg (or corresponding placebo) during week 3. Liraglutide and placebo were administered subcutaneously into the abdomen.

For flexibility for the enrolled subjects, 14 to 42 days were allowed between each crossover period. In each crossover period, subjects attended the study site for the drug–drug interaction investigation after 5 days of daily dosing with liraglutide 1.8 mg or corresponding placebo. On the drug–drug investigation day, a single oral tablet of the contraceptive was
administered with 100 mL of water 7 hours after the administration of liraglutide/placebo, whereby the maximum concentration of ethinyl estradiol and levonorgestrel was planned to coincide with the time of \( C_{\text{max}} \) of liraglutide and thus establish optimal potential for drug–drug interaction. On this day, subjects had breakfast following administration of liraglutide/placebo in the morning. Two hours before and 2 hours after administration of the contraceptive, subjects received a small meal (high carbohydrate, low protein, low fat content). With the first meal, subjects were given 200 mL of water and were allowed to drink water with the last meal. Serum concentrations of ethinyl estradiol/levonorgestrel were followed for 74 hours after administration of the contraceptive to aim for coverage at least 80% of total AUC for both components. Daily dosing with liraglutide or placebo was continued during the blood sampling period.

Bioanalytical Methods

For determination of serum concentrations of ethinyl estradiol and levonorgestrel, 13 blood samples (7 mL each) were drawn on each of the drug–drug investigation visits; before dose (−15 minutes) and at 0.5, 1, 2, 3, 4, 6, 8, 12, 17, 24, 48, and 74 hours post administration of the contraceptive. Samples were stored at −20°C until analyzed using gas chromatography/mass spectrometry at AAI Pharma Deutschland GmbH & KG (now Nuvisan, Neu-Ulm, Germany). Lower limit of quantification (LLOQ) levels for the bioanalysis methods were 2.5 pg/mL for ethinyl estradiol and 50.0 pg/mL for levonorgestrel. For each sample, 1.00 mL of human serum was aliquoted and spiked with 25.0 µL of the internal standard solution. For ethinyl estradiol, an isotope-labeled analog (D4-ethinyl estradiol) was the internal standard, whereas for levonorgestrel it was norethindrone. The samples were acidified with phosphoric acid and extracted into toluene. After evaporation of the toluene phase, the samples were reconstituted in dichloromethane and washed with an aqueous sodium hydroxide solution. Finally, the dichloromethane phase was transferred to new sample tubes and further used for derivatization. The sample extracts were evaporated to dryness and derivatized in 2 steps in order to transfer both analytes into suitable derivatives for gas chromatographic separation and mass spectrometric detection. The samples were injected into a Trio 2000 GC/MS system (Phenomenex, Torrance, California) was used for chromatographic separation. The injector temperature was set to 260°C and the temperature program was set to 170°C (1 minute), followed by a 15°C/min ramp to 340°C; then 340°C was held for 2 minutes. The mass spectrometer was operated in the chemical ionization mode, using ammonia as reagent gas. Negative ions were detected at the following m/z ratios: ethinyl estradiol (m/z 490), levonorgestrel (m/z 299), D4-ethinyl estradiol (IS1) m/z 494), norethindrone (IS2) (m/z 285).

The interbatch precision (percent coefficient of variation, CV%) for ethinyl estradiol varied between 6.06% and 3.50% for quality control (QC) levels 30.0 to 400 pg/mL (and between 4.94 and 3.32 CV% for QC levels 7.50-100 pg/mL). Correspondingly, the accuracy varied between 0.85% to 0.36% and 0.93% to −0.51%, respectively. The precision (CV%) for levonorgestrel measurements varied from 3.62% to 4.45%, whereas the accuracy ranged from 5.03% to −7.65% for QC levels ranging between 150 and 20 000 pg/mL.

Similarly, 3-mL blood samples for the determination of the plasma concentrations of liraglutide were collected at the drug–drug interaction visits. Nine blood samples were collected at each visit post administration of liraglutide. Samples were analyzed using an enzyme-linked immunosorbent assay10 (Unilabs, Copenhagen, Denmark) to measure the total concentration of liraglutide. The repeatability was 2.4% to 6.5%, the day-to-day variation was 3.7% to 10%, the LLOQ was 18 pM, and the dilution was documented up to 16-fold while maintaining linearity.

Pharmacokinetic Assessment and Statistical Analyses

Estimation of pharmacokinetic end points used data from exposed subjects with at least 1 evaluable pharmacokinetic profile of ethinyl estradiol or levonorgestrel. In addition to this criterion, subjects had fulfilled the inclusion/exclusion criteria and had not been in violation of the study protocol. End points were derived from the serum ethinyl estradiol and levonorgestrel concentrations and actual times by noncompartmental method (model 200 for extravascular administration of WinNonlin Professional 4.1.1b; Pharsight Inc, Mountain View, California).

Pharmacokinetic end points included area under the serum ethinyl estradiol and levonorgestrel concentration–time curves from 0 to infinity (AUC) and AUC from 0 to 48 hours (AUC\(_0\)–48h) for ethinyl estradiol and
from 0 to 74 hours (AUC\textsubscript{0-74}, for levonorgestrel), C\textsubscript{max}, t\textsubscript{max}, apparent total plasma clearance (CL/F), elimination half-life (t\textsubscript{1/2}), and apparent volume of distribution (Vz/F). C\textsubscript{max} and t\textsubscript{max} were obtained as the observed values, and AUC was determined using standard noncompartmental methods (the trapezoidal method).

The primary end point was the AUC for ethinyl estradiol and levonorgestrel, and exposures during liraglutide and placebo were declared equivalent if the 90% confidence interval (CI) for the ratios of AUC was contained within the limits 0.80 to 1.25. Comparison between liraglutide and placebo was performed for ethinyl estradiol and levonorgestrel, respectively, by use of a linear normal model (analysis of variance) for the log-transformed values of AUC. The model included effects of period and treatment and a random effect of subject. Secondary pharmacokinetic end points were analyzed in a similar way to the primary pharmacokinetic end point except for the estimated difference for t\textsubscript{max}.

Safety Assessments

Safety assessments involved recording of adverse events before and throughout the study, between crossover periods, and after completion of dosing evaluations of vital signs, ECG, hematology, and clinical chemistry analysis.

RESULTS

All 21 enrolled women were Caucasian, postmenopausal, and between 51 and 71 years old. At baseline, age, body weight, and BMI (all mean ± standard deviation) were 58 ± 5 years, 68.8 ± 10.8 kg, and 24.6 ± 3.3 kg/m\textsuperscript{2}, respectively.

Pharmacokinetics of Ethinyl Estradiol and Levonorgestrel

**Ethinyl estradiol.** Figure 1a shows the mean serum concentration–time profile and Table I shows the mean pharmacokinetic end points of ethinyl estradiol coadministered with liraglutide (at steady state) and with placebo.

AUC for ethinyl estradiol was equivalent (during liraglutide/placebo), as the 90% CI for the estimated ratio was within the prespecified limits for equivalence, that is, 0.80 to 1.25. The effect of period was not statistically significant. Furthermore, equivalence was shown with respect to AUC\textsubscript{0-48h} and Vz/F but was not demonstrated for C\textsubscript{max} and t\textsubscript{1/2} (Table II). C\textsubscript{max} and t\textsubscript{1/2} were estimated to be 12% and 2% lower, respectively, during liraglutide steady-state conditions than during placebo. In addition, the t\textsubscript{max} for ethinyl estradiol occurred 1.5 hours later with liraglutide treatment than with placebo.

**Levonorgestrel.** Figure 1b shows the mean serum concentration–time profile and Table I the pharmacokinetic end points of levonorgestrel following the contraceptive being given at liraglutide steady state and with placebo. For AUC, equivalence was not demonstrated for levonorgestrel, being 18% larger with liraglutide compared with placebo (Table II). However, for a number of subjects AUC was not calculated. Prior to unblinding the treatment code it was evaluated that these profiles had too flat an elimination phase for the AUC to be extrapolated to infinity. This happened equally frequently for liraglutide and placebo administration (9 profiles in each group). The effect of period was not statistically significant. All subjects had quantifiable serum concentrations of

![Figure 1. Mean concentration–time profiles during treatment with liraglutide or placebo for (a) ethinyl estradiol (n = 21) and (b) levonorgestrel (n = 21).](attachment:image_url)
Liraglutide exposure. As liraglutide was only administered with ethinyl estradiol/levonorgestrel, no comparative data are available. The bioanalysis of liraglutide confirmed that liraglutide and placebo were dosed as planned.

Safety

More adverse events were reported with liraglutide treatment than with placebo. The most predominant events reported with liraglutide were of gastrointestinal origin, for example, nausea, eructation, abdominal pain, constipation, and dyspepsia. No subjects withdrew from the study.

DISCUSSION

This study was designed to examine the effects of liraglutide on the pharmacokinetic absorption properties of the components of an oral contraceptive drug combining 0.03 mg of ethinyl estradiol and 0.15 mg of levonorgestrel, both of which are widely used as contraceptive compounds. Both compounds are used in a low dose to reduce the risk of adverse effects, so it is important to examine whether liraglutide has the potential to lower their bioavailability, thereby compromising their contraceptive efficacy. As in other drug–drug interaction studies, the contraceptive product used in this study contains 0.03 mg of ethinyl estradiol. Contraceptive products containing lower doses of ethinyl estradiol (eg, 0.02 mg) have not been investigated in this study.

Liraglutide had no effect on the bioavailability of ethinyl estradiol when the contraceptive drug was administered with liraglutide and with placebo. Although equivalence was not demonstrated for levonorgestrel AUC, exposure was not lower when given with liraglutide. However, AUC was not calculated for a number of subjects because of a flat elimination phase. In contrast, the partial AUC (AUC₀-₄₈) was calculated for all subjects, and for this end point equivalence was shown for levonorgestrel, with a fairly similar estimated ratio in exposure between liraglutide and placebo as shown in the analysis of AUC. Thus, based on these observations one may conclude that liraglutide did not lower the bioavailability (shown as AUC) of either ethinyl estradiol or levonorgestrel.

For the remaining pharmacokinetic end points, Cmax for both ethinyl estradiol and levonorgestrel was lower (12% and 13%, respectively) and t₁/₂ was slightly shorter during liraglutide treatment, with neither of these pharmacokinetic end points equivalent when compared during treatment with liraglutide and placebo. This corresponded to a minor right-shift in the concentration–time curves and a later tₘₐₓ (1.5 hours). The slightly lower Cmax and

Table I  Mean Pharmacokinetic End Points for Ethinyl Estradiol and Levonorgestrel With Liraglutide Or Placebo

<table>
<thead>
<tr>
<th></th>
<th>Ethinyl Estradiol</th>
<th>Levonorgestrel</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC, h·pg/mL</td>
<td>856 (226)</td>
<td>63 153 (25 496)</td>
</tr>
<tr>
<td>AUC₀-₇₄, h·pg/mL</td>
<td>752 (171)</td>
<td>47 150 (24 260)</td>
</tr>
<tr>
<td>Cmax, pg/mL</td>
<td>51.5 (17.7)</td>
<td>3073 (1791)</td>
</tr>
<tr>
<td>tₘₐₓ, h</td>
<td>3.0 (2.0-12.0)</td>
<td>3.0 (1.0-8.0)</td>
</tr>
<tr>
<td>t₁/₂, h</td>
<td>14.9 (6.2)</td>
<td>32.6 (9.8)</td>
</tr>
<tr>
<td>CL/F, L/h</td>
<td>37.9 (12.1)</td>
<td>2.9 (1.4)</td>
</tr>
<tr>
<td>Vz/F, L</td>
<td>720.5 (193.8)</td>
<td>113.7 (68.3)</td>
</tr>
</tbody>
</table>

AUC, area under the curve; AUC₀-₄₈, AUC from 0 to 74 hours; Cmax, maximum concentration; CL/F, apparent total plasma clearance; tₘₐₓ, time to maximum concentration; t₁/₂, half-life; Vz/F, apparent volume of distribution. Values are mean (standard deviation) except for tₘₐₓ, which is given as median (minimum–maximum).

a.Ethinyl estradiol, n = 20 (liraglutide) and n = 19 (placebo) for AUC, CL/F, Vz/F.
b.Levonorgestrel n = 12 (liraglutide and placebo) for AUC, CL/F, Vz/F.
c.AUC₀-₄₈ for ethinyl estradiol and AUC₀-₄₈ for levonorgestrel.
delayed t_{max} for both ethinyl estradiol and levonorgestrel when given concomitantly with liraglutide are consistent with the minor delay in the rate of gastric emptying reported with liraglutide.\textsuperscript{13} That the total exposures (AUC) of ethinyl estradiol and levonorgestrel are not lowered during liraglutide treatment is important for the contraceptive effect to be unaffected. From the right-shifted ethinyl estradiol and levonorgestrel concentration–time curves, it further follows that the minimum concentrations of ethinyl estradiol and levonorgestrel with liraglutide treatment are not lower than with placebo and thus the concentrations do not fall below the threshold concentration for contraceptive effect.

A similar study evaluated exenatide coadministration (10 µg given twice daily) on the pharmacokinetics of 0.03 mg of ethinyl estradiol and 0.15 mg of levonorgestrel administered (as an oral combination contraceptive drug) 30 minutes after exenatide administration or 1 hour before as single- and multiple-dose administrations.\textsuperscript{21} The results were similar to those observed with liraglutide, with no significant changes of AUC found. Exenatide reduced C_{max} and prolonged t_{max} when the oral contraceptive drug was administered after exenatide administration. No major changes in the pharmacokinetic profiles of ethinyl estradiol or levonorgestrel were observed when the oral contraceptive drug was dosed 1 hour before administration of exenatide.\textsuperscript{21}

### Table II  Comparison Between Treatments (Liraglutide/Placebo) for Ethinyl Estradiol and Levonorgestrel

<table>
<thead>
<tr>
<th></th>
<th>Ethinyl Estradiol</th>
<th>Levonorgestrel</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Liraglutide/Placebo (n = 21)</td>
<td>Liraglutide/Placebo (n = 21)</td>
</tr>
<tr>
<td>AUC Estimate</td>
<td>1.06</td>
<td>1.18</td>
</tr>
<tr>
<td>90% CI</td>
<td>0.99-1.13</td>
<td>1.04-1.34</td>
</tr>
<tr>
<td>AUC_{0-t} \textsuperscript{b} Estimate</td>
<td>1.06</td>
<td>1.15</td>
</tr>
<tr>
<td>90% CI</td>
<td>1.00-1.11</td>
<td>1.06-1.24</td>
</tr>
<tr>
<td>C_{max} Estimate</td>
<td>0.88</td>
<td>0.87</td>
</tr>
<tr>
<td>90% CI</td>
<td>0.79-0.97</td>
<td>0.75-1.00</td>
</tr>
<tr>
<td>t_{max}, h Estimate</td>
<td>1.5</td>
<td>1.5</td>
</tr>
<tr>
<td>90% CI</td>
<td>1.0-2.5</td>
<td>0.5-2.0</td>
</tr>
<tr>
<td>t_{1/2} Estimate</td>
<td>0.98</td>
<td>0.96</td>
</tr>
<tr>
<td>90% CI</td>
<td>0.79-1.23</td>
<td>0.90-1.03</td>
</tr>
<tr>
<td>Vz/F Estimate</td>
<td>0.96</td>
<td>0.85</td>
</tr>
<tr>
<td>90% CI</td>
<td>0.87-1.07</td>
<td>0.76-0.96</td>
</tr>
</tbody>
</table>

AUC, area under the curve; AUC_{0-t}, AUC from 0 to 74 hours; CI, confidence interval; C_{max}, maximum concentration; t_{max}, time to maximum concentration; t_{1/2}, half-life; Vz/F, apparent volume of distribution

\textsuperscript{a}“Estimates” are the ratio or difference (as for t_{max}) between liraglutide and placebo treatments. CL/F not shown as results correspond to analyses for AUC (CL/F = dose/AUC).

\textsuperscript{b}AUC_{max} for ethinyl estradiol and AUC_{max} for levonorgestrel.

Consistent with recent confirmatory clinical studies with liraglutide, the most frequently reported adverse events in this study were gastrointestinal related, some of which could potentially have a detrimental effect on the absorption—and therefore efficacy—of the oral contraceptive. However, gastrointestinal side effects with liraglutide are mostly transient and tend to decline after 4 weeks.\textsuperscript{4-9} This study was performed in postmenopausal (nonreproductive) women with relatively normal BMI and not in women of reproductive age with type 2 diabetes, who are likely to have higher BMIs. Postmenopausal women were selected for this study to avoid the potential effect of hormonal fluctuations in a younger population on the interpretation of the pharmacokinetics. The pharmacokinetics of a similar combination oral contraceptive containing ethinyl estradiol (0.02 mg) and drospirenone (3 mg) have been previously studied in healthy postmenopausal women, and results were consistent with published reports in healthy young women.\textsuperscript{22} This suggests that the pharmacokinetics of this type of combined oral contraceptive are likely to be similar in postmenopausal and women of reproductive age. Similarly, the impact of obesity on the pharmacokinetics of a similar oral contraceptive containing ethinyl estradiol (0.02 mg) and levonorgestrel (0.1 mg) has previously been investigated. No differences in ethinyl estradiol or levonorgestrel volume of distribution were
found between obese subjects and subjects with normal BMI. The half-life of levonorgestrel was doubled in the obese subjects, leading to longer time to reach steady state. This could potentially result in a detrimental effect on the efficacy of the oral contraceptive. In our study, however, the half-lives of ethinyl estradiol and levonorgestrel were slightly shorter with liraglutide coadministration, suggesting that steady-state levels of ethinyl estradiol and levonorgestrel will not be later with liraglutide. Overall, this study indicates no clinically relevant decrease in overall bioavailability, that is, exposure of ethinyl estradiol (0.03 mg) or levonorgestrel (0.15 mg), when this contraceptive drug is coadministered with liraglutide 1.8 mg at steady state in postmenopausal healthy women.

We thank the investigators and their staff for the conduct of the study and the research volunteers for the participation. We thank Bernhard Schmid at Nuvisan for bioanalysis of ethinyl estradiol and levonorgestrel and helpful comments during reporting. The authors take full responsibility for this article but acknowledge Watermeadow Medical UK (supported by Novo Nordisk A/S) for writing assistance.

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REFERENCES

20. European Medicines Agency (EMEA). Note for guidance on
the investigation of drug interactions. CPMP/EWP/560/95, 17
cmacokinetics of a combination oral contraceptive in healthy women.
22. Blode H, Schürmann R, Benda N. Novel ethinyl estradiol-
beta-cyclodextrin clathrate formulation does not influence the
relative bioavailability of ethinyl estradiol or coadministered
oral contraceptive pharmacokinetics and hypothalamic-pituitary-

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