symptomatic hypoglycemia occurred in 85% and 80% of patients when Trulicity 0.75 mg and 1.5 mg, respectively, was co-administered with prandial insulin. Severe hypoglycemia occurred in 2.4% and 3.4% of patients when Trulicity 0.75 mg, and 1.5 mg, respectively, was co-administered with prandial insulin. *Heart Rate Increase and Tachycardia Related Adverse Reactions*: Trulicity 0.75 mg and 1.5 mg resulted in a mean increase in heart rate (HR) of 2-4 beats per minute (bpm). The long-term clinical effects of the increase in HR have not been established. Adverse reactions of sinus tachycardia were reported more frequently in patients exposed to Trulicity. Sinus tachycardia was reported in 3.0%, 2.8%, and 5.6% of patients treated with placebo, Trulicity 0.75 mg, and Trulicity 1.5 mg, respectively. Persistence of sinus tachycardia (reported at more than 2 visits) was reported in 0.2%, 0.4%, and 1.6% of patients treated with placebo, Trulicity 0.75 mg and Trulicity 1.5 mg, respectively. Episodes of sinus tachycardia, associated with a concomitant increase from baseline in heart rate of ≥15 beats per minute, were reported in 0.7%, 1.3%, and 2.2% of patients treated with placebo, Trulicity 0.75 mg, and Trulicity 1.5 mg, respectively. *Immunogenicity*: Across four Phase 2 and five Phase 3 clinical studies, 64 (1.6%) Trulicity-treated patients developed anti-drug antibodies (ADAs) to the active ingredient in Trulicity (ie, dulaglutide). Of the 64 dulaglutide-treated patients that developed dulaglutide ADAs, 34 patients (0.9% of the overall population) had dulaglutide-neutralizing antibodies, and 36 patients (0.9% of the overall population) developed antibodies against native GLP-1. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, the incidence of antibodies to dulaglutide cannot be directly compared with the incidence of antibodies of other products. *Hypersensitivity*: Systemic hypersensitivity adverse reactions sometimes severe (eg, severe urticaria, systemic rash, facial edema, lip swelling) occurred in 0.5% of patients on Trulicity in the four Phase 2 and Phase 3 studies. *Injection-site Reactions*: In the placebo-controlled studies, injection-site reactions (eg, injection-site rash, erythema) were reported in 0.5% of Trulicity-treated patients and in 0.0% of placebo-treated patients. *PR Interval Prolongation and Adverse Reactions of First Degree Atrioventricular (AV) Block*: A mean increase from baseline in PR interval of 2-3 milliseconds was observed in Trulicity-treated patients in contrast to a mean decrease of 0.9 millisecond in placebo-treated patients. The adverse reaction of first degree AV block occurred more frequently in patients treated with Trulicity than placebo (0.9%, 1.7%, and 2.3% for placebo, Trulicity 0.75 mg, and Trulicity 1.5 mg, respectively). On electrocardiograms, a PR interval increase to at least 220 milliseconds was observed in 0.7%, 2.5%, and 3.2% of patients treated with placebo, Trulicity 0.75 mg, and Trulicity 1.5 mg, respectively. *Amylase and Lipase Increase*: Patients exposed to Trulicity had mean increases from baseline in lipase and/or pancreatic amylase of 14% to 20%, while placebo-treated patients had mean increases of up to 3%. **Postmarketing Experience**: Anaphylactic reactions have been reported during post-approval use of Trulicity. Because these events are reported voluntarily from a population of uncertain size, it is generally not possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

DRUG INTERACTIONS

Trulicity slows gastric emptying and thus has the potential to reduce the rate of absorption of concomitantly administered oral medications. Caution should be exercised when oral medications are concomitantly administered with Trulicity. Drug levels of oral medications with a narrow therapeutic index should be adequately monitored when concomitantly administered with Trulicity. In clinical pharmacology studies, Trulicity did not affect the absorption of the tested, orally administered medications to any clinically relevant degree.

USE IN SPECIFIC POPULATIONS

Pregnancy: Risk Summary Limited data with Trulicity in pregnant women are not sufficient to determine a drug associated risk for major birth defects and miscarriage. Based on animal reproduction studies, there may be risks to the fetus from exposure to dulaglutide during pregnancy. Trulicity should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. In pregnant rats administered dulaglutide during organogenesis, early embryonic deaths, fetal growth reductions, and fetal abnormalities occurred at systemic exposures at least 14-times human exposure at the maximum recommended human dose (MRHD) of 1.5 mg/week. In pregnant rabbits administered dulaglutide during organogenesis, major fetal abnormalities occurred at 13-times human exposure at the MRHD. Adverse embryo/fetal effects in animals occurred in association with decreased maternal weight and food consumption attributed to the pharmacology of dulaglutide.
Lactation: Risk Summary There are no data on the presence of dulaglutide in human milk, the effects on the breastfed infant, or the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Trulicity and any potential adverse effects on the breastfed infant from Trulicity or from the underlying maternal condition. **Pediatric Use:** Safety and effectiveness of Trulicity have not been established in pediatric patients. Trulicity is not recommended for use in pediatric patients younger than 18 years. **Geriatric Use:** In the pool of placebo- and active-controlled trials, 620 (18.6%) Trulicity-treated patients were 65 years of age and over and 65 Trulicity-treated patients (1.9%) were 75 years of age and over. No overall differences in safety or efficacy were detected between these patients and younger patients, but greater sensitivity of some older individuals cannot be ruled out. **Hepatic Impairment:** There is limited clinical experience in patients with mild, moderate, or severe hepatic impairment. Therefore, Trulicity should be used with caution in these patient populations. In a clinical pharmacology study in subjects with varying degrees of hepatic impairment, no clinically relevant change in dulaglutide pharmacokinetics (PK) was observed. **Renal Impairment:** In the four Phase 2 and five Phase 3 randomized clinical studies, at baseline, 50 (1.2%) Trulicity-treated patients had mild renal impairment (eGFR ≥60 but <90 mL/min/1.73 m^2), 171 (4.3%) Trulicity-treated patients had moderate renal impairment (eGFR ≥30 but <60 mL/min/1.73 m^2) and no Trulicity-treated patients had severe renal impairment (eGFR <30 mL/min/1.73 m^2). No overall differences in safety or effectiveness were observed relative to patients with normal renal function, though conclusions are limited due to small numbers. In a clinical pharmacology study in subjects with renal impairment including end-stage renal disease (ESRD), no clinically relevant change in dulaglutide PK was observed. There is limited clinical experience in patients with severe renal impairment or ESRD. Trulicity should be used with caution, and if these patients experience adverse gastrointestinal side effects, renal function should be closely monitored. **Gastroparesis:** Dulaglutide slows gastric emptying. Trulicity has not been studied in patients with pre-existing gastroparesis.

OVERDOSAGE

Overdoses have been reported in clinical studies. Effects associated with these overdoses were primarily mild or moderate gastrointestinal events (eg, nausea, vomiting) and non-severe hypoglycemia. In the event of overdose, appropriate supportive care (including frequent plasma glucose monitoring) should be initiated according to the patient's clinical signs and symptoms.

PATIENT COUNSELING INFORMATION See FDA-approved Medication Guide

• Inform patients that Trulicity causes benign and malignant thyroid C-cell tumors in rats and that the human relevance of this finding has not been determined. Counsel patients to report symptoms of thyroid tumors (eg, a lump in the neck, persistent hoarseness, dysphagia, or dyspnea) to their physician. • Inform patients that persistent severe abdominal pain, that may radiate to the back and which may (or may not) be accompanied by vomiting, is the hallmark symptom of acute pancreatitis. Instruct patients to discontinue Trulicity promptly, and to contact their physician, if persistent severe abdominal pain occurs. • The risk of hypoglycemia may be increased when Trulicity is used in combination with a medicine that can cause hypoglycemia, such as a sulfonylurea or insulin. Review and reinforce instructions for hypoglycemia management when initiating Trulicity therapy, particularly when concomitantly administered with a sulfonylurea or insulin. • Patients treated with Trulicity should be advised of the potential risk of dehydration due to gastrointestinal adverse reactions and take precautions to avoid fluid depletion. Inform patients treated with Trulicity of the potential risk for worsening renal function and explain the associated signs and symptoms of renal impairment, as well as the possibility of dialysis as a medical intervention if renal failure occurs. • Inform patients that serious hypersensitivity reactions have been reported during postmarketing use of Trulicity and other GLP-1 receptor agonists. If symptoms of hypersensitivity reactions occur, patients must stop taking Trulicity and seek medical advice promptly. • Advise patients to inform their healthcare provider if they are pregnant or intend to become pregnant. • Prior to initiation of Trulicity, train patients on proper injection technique to ensure a full dose is delivered. Refer to the accompanying Instructions for Use for complete administration instructions with illustrations. • Inform patients of the potential risks and benefits of Trulicity and of alternative modes of therapy. Inform patients about the importance of adherence to dietary instructions, regular physical activity, periodic blood glucose monitoring and HbA1c testing, recognition and management of hypoglycemia and hyperglycemia, and assessment for diabetes complications. During periods of stress such as fever, trauma, infection, or surgery, medication requirements may change and advise patients to seek medical advice promptly. • Each weekly dose of Trulicity can be administered at any time of day, with or without food. The day of once-weekly administration can be changed if necessary, as long as the last dose was administered 3 or more days before. If a dose is missed and there are at least 3 days (72 hours) until the next scheduled dose, it should be administered as soon as possible. Thereafter, patients can resume their usual once-weekly dosing schedule. If a dose is missed and the next regularly scheduled dose is due in 1 or 2 days, the patient should not administer the missed dose and instead resume Trulicity with the next regularly scheduled dose. • Advise patients treated with Trulicity of the potential risk of gastrointestinal side effects. • Instruct patients to read the Medication Guide and the Instructions for Use before starting Trulicity therapy and review them each time the prescription is refilled. • Instruct patients to inform their doctor or pharmacist if they develop any unusual symptom, or if any known symptom persists or worsens. • Inform patients that response to all diabetic therapies should be monitored by periodic measurements of blood glucose and HbA1c levels, with a goal of decreasing these levels towards the normal range. HbA1c is especially useful for evaluating long-term glycemic control.

Lilly

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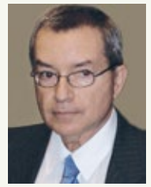
Additional information can be found at www.trulicity.com

DG HCP BS 10FEB2017

Trulicity® (dulaglutide) DG HCP BS 10FEB2017 7 x 9.5

Enfermedad hepática grasa no alcohólica (*NAFLD*)



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Una muy activa abogada de alrededor de 50 años de edad, ligeramente obesa (BMI: 31.5), completamente asintomática y abstemia, se sometió a varias pruebas de laboratorio indicados después de comprobarse, a la palpación externa, una discreta hepatomegalia poco dolorosa. Sorpresivamente, aparecieron cifras de aminotransferasa y fosfatasa alcalina medianamente elevadas. Un estudio ultrasonográfico posterior demostró la presencia de una enfermedad hepática grasa no alcohólica o esteatosis hepática.

¿Qué significa esto? Se estima estadísticamente que la enfermedad hepática grasa no alcohólica (*nonalcoholic fatty liver disease, NAFLD*) afecta entre el 20 y el 25% de la población adulta norteamericana. Las personas obesas mórbidas la padecen por encima del 40%.

Aunque su etiología no siempre queda clara, se invocan como desencadenantes de la esteatosis hepática la obesidad (probablemente la causa del exagerado incremento de la *NAFLD* en los últimos 30 años), la diabetes mellitus tipo II, la hipertrigliceridemia, el uso habitual de corticosteroides, tamoxifeno, diltiazem, amiodarona, drogas antirretrovirales y otros medicamentos, la relación con químicos como el tetracloruro de carbono y los derivados del fósforo, ciertas endocrinopatías como la enfermedad de Cushing y el hipopituitarismo, los ovarios poliquísticos, la apnea obstructiva de sueño, el consumo excesivo de fructosa en refrescos, los trastornos alimenticios con cambios bruscos de peso corporal y la nutrición parenteral. Se ha señalado la probable relación de la condición con la actividad de un gen que codifica la apolipoproteína C3.

Se ha observado también un incremento de esta patología hepática en personas que padecen manifestaciones psoriásicas. Por supuesto, el hallazgo de *NAFLD* es casi constante (entre 6 y 11 veces más) en personas con síndrome metabólico (resistencia a la insulina, obesidad abdominal, hipertrigliceridemia e hipertensión arterial). El alcoholismo es, obviamente, una causa a tener en cuenta (*AFLD*), pero sin olvidar que no es un requisito indispensable de esta afección.

En la anatomía patológica –por biopsia hepática– se describen formas macrovesiculares y una microvesicular de la *NAFLD*. La forma microvesicular –menos común– suele observarse en el síndrome de Reye, la toxicidad por didanosina, ácido valproico, altas dosis de tetraciclina y en el hígado graso agudo del embarazo. Esta forma es menos frecuente, pero reviste más peligrosidad, pues tiende a la esteatohepatitis no alcohólica (*NASH*), que cursa con inflamación, fibrosis y la posibilidad de un fallo hepático subagudo o, incluso, fulminante. La *NASH* es la tercera causa de cirrosis y cáncer hepático en los Estados Unidos, después de la hepatitis C y del alcoholismo.

Aunque hemos comenzado esta breve revisión con el ejemplo de una paciente con pruebas de laboratorio alteradas, en realidad suelen ser normales en hasta un 80% de los casos al inicio. La ultrasonografía, el CT y el MRI son útiles, pero no definen la diferencia entre la *NAFLD* y la *NASH*. La espectroscopía por resonancia magnética es más precisa, pero no sustituye a la biopsia hepática percutánea.

Si los factores de riesgo y los desencadenantes de la *NAFLD* son debidamente controlados, el pronóstico es bueno a largo plazo e, incluso, reversible. De no ser así, el riesgo de cirrosis se eleva hasta un 50% en 10 años. La *NAFLD* es más común en el sexo femenino, pero mucho más peligrosa en el masculino. Se ha descrito la *NAFLD* en hígados trasplantados. El tratamiento depende de las causas etiológicas y debe ser controlado por un especialista.