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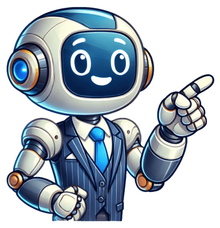

Postal address: Norwegian Institute of Public Health WHO Collaborating Centre for Drug Statistics Methodology Postboks 222 Skøyen 0213 Oslo NorwayVisiting/delivery address: Myrens verksted 6H 0473 Oslo Norway Tel: +47 21 07 81 60E-mail: 08-08-2024 Team Medicover General Medicine Diabetes is a chronic condition that affects millions of people worldwide. The disease manifests in two primary types: type 1 and type 2, with the latter being more prevalent among adults. Type 2 diabetes is characterized by the body's inability to use insulin, leading to elevated blood sugar levels effectively. Managing this condition often requires a combination of lifestyle changes and medications. One of the effective treatments for managing type 2 diabetes is the Liraglutide injection. In this article, we will explore the benefits of Liraglutide, its mechanism of action, potential side effects, and its recommended dosage. Get a second opinion from trusted experts and makeconfident, informed decisions. Get Second Opinion What is Liraglutide? Liraglutide is a medication used to treat type 2 diabetes and is marketed under the brand name Victoza. This drug is part of a class of medications known as GLP-1 receptor agonists. GLP-1 receptor agonists work by mimicking the function of the glucagon-like peptide-1 hormone, which has a crucial role in regulating blood sugar levels. When used in conjunction with diet and exercise, this medication helps improve blood sugar control in adults with type 2 diabetes. Unlike some other diabetes medications, Liraglutide offers the added benefit of aiding in weight loss, making it a multifaceted treatment option. The medication is delivered via injection, which allows for a more controlled release into the bloodstream. This method of administration ensures that the drug can act efficiently to manage blood glucose levels, providing a more stable and effective treatment for diabetes patients. How Does Liraglutide Work? Liraglutide Mechanism of Action Liraglutide mimics the action of the hormone glucagon-like peptide-1 (GLP-1), which is naturally produced in the intestines. GLP-1 has several functions that help regulate blood sugar levels, making it a potent tool in diabetes management: Stimulates Insulin Secretion: Liraglutide helps the pancreas release insulin in response to high blood sugar levels. This action is crucial for lowering blood glucose and preventing hyperglycemia. Inhibits Glucagon Release:It reduces the amount of glucagon, a hormone that raises blood sugar levels. By inhibiting glucagon, Liraglutide helps maintain a balance in blood sugar levels. Slows Gastric Emptying: By slowing down stomach emptying, Liraglutide helps regulate the absorption of sugar into the bloodstream. This delayed absorption can prevent spikes in blood sugar levels after meals. Promotes Satiety:It acts on the brain to promote a feeling of fullness, which can help with weight loss. Reduced appetite means fewer calories consumed, which is beneficial for weight management. Benefits of Liraglutide Injection Improved Blood Sugar Control One of the primary benefits of Liraglutide is its ability to improve blood sugar control. By stimulating insulin secretion and inhibiting glucagon release, it helps maintain blood glucose levels within a target range. This dual action makes it highly effective in reducing HbA1c levels, a key indicator of long-term blood sugar control. Consistent management of blood glucose levels can prevent the complications associated with diabetes, such as neuropathy, retinopathy, and nephropathy. Weight Loss Liraglutide has been shown to promote weight loss in patients with type 2 diabetes. The medication acts on the brain to create a feeling of fullness, reducing overall calorie intake. This is particularly beneficial for individuals with type 2 diabetes, as excess weight can exacerbate insulin resistance. Weight loss can be helpful for people with type 2 diabetes as it can help improve insulin sensitivity and blood sugar control. Multiple studies have confirmed that patients taking Liraglutide experience significant weight reduction compared to those on other treatments. Cardiovascular Benefits Studies have shown that Liraglutide can reduce the risk of major cardiovascular events, such as heart attack and stroke, in people with type 2 diabetes who have a high risk of heart disease. This adds a layer of protection for patients who are already at an increased risk of cardiovascular issues. The cardiovascular benefits of Liraglutide make it an attractive option for comprehensive diabetes management. The medication's ability to lower blood pressure and improve lipid profiles further contributes to its cardiovascular protective effects. Potential Side Effects of liraglutide injection Common Side Effects As with any medication, Liraglutide can cause side effects. Some of the most common side effects include: Nausea Diarrhea Vomiting Decreased appetite Indigestion These side effects are usually mild and tend to diminish as the body adjusts to the medication. However, it is essential to monitor any persistent or severe symptoms and report them to your healthcare provider. Managing these side effects may involve dose adjustments or additional supportive treatments. Serious Side Effects While rare, some severe side effects can occur. These may include: Pancreatitis:Symptoms include severe abdominal pain that may radiate to the back, nausea, and vomiting. Pancreatitis is a potentially life-threatening condition that requires immediate medical attention. Gallbladder Disease: Symptoms include pain in the upper right side of the abdomen, fever, nausea, and vomiting. Gallbladder issues can lead to complications that may require surgical intervention. Kidney Problems:Symptoms include changes in urination, swelling in the feet or ankles, and fatigue. If not promptly addressed, kidney issues can escalate to chronic kidney disease. If you experience any of these severe side effects, it is essential to seek medical attention immediately. Early intervention can prevent complications and ensure the safe use of Liraglutide. Liraglutide Injection Dosage Starting Dose The typical starting dose of Liraglutide is 0.6 mg once daily. This dose is usually maintained for at least one week to allow the body to adjust to the medication. During this initial phase, patients may experience mild side effects as their body becomes accustomed to the drug. Maintenance Dose After the initial week, the dose is usually increased to 1.2 mg once daily. If further blood sugar control is needed, the dose may be increased to 1.8 mg once daily. This incremental dosing helps to minimize side effects while optimizing blood sugar control. Regular monitoring of blood glucose levels is essential to determine the effectiveness of the dosage. How to Administer Liraglutide Liraglutide is administered as a subcutaneous injection, which means it is injected under the skin. The injection can be given in the abdomen, thigh, or upper arm. It is important to rotate injection sites to avoid irritation. Proper administration techniques should be followed to ensure the medication's efficacy and reduce the risk of injection-site reactions. Liraglutide Injection Brand Name Liraglutide is marketed under the brand name Victoza. It is available in pre-filled pens that are easy to use and provide accurate dosing. These pens come with clear instructions and are designed for patient convenience. Victoza injection is a prescription medication, so it is essential to consult with a healthcare provider to determine if it is the right treatment option for you. Your healthcare provider will guide you on how to use the injection pen correctly and monitor your progress regularly. Conclusion Liraglutide injection offers numerous benefits for individuals with type 2 diabetes, including improved blood sugar control, weight loss, and cardiovascular protection. While it can cause side effects, the potential benefits often outweigh the risks for many patients. It is essential to follow the prescribed dosage and consult with a healthcare provider to ensure the best possible outcome. By understanding the benefits and potential side effects of Liraglutide, you can make an informed decision about whether this medication is proper for you. Always work closely with your healthcare provider to manage your diabetes effectively and maintain a healthy lifestyle. Adequate management of diabetes involves a comprehensive approach that includes medication, diet, exercise, and regular monitoring. Frequently Asked Questions To inject liraglutide, use the prefilled pen to administer the medication subcutaneously into your abdomen, thigh, or upper arm. Rotate injection sites to avoid irritation and follow the instructions provided with the pen. Liraglutide helps with weight loss by reducing appetite and calorie intake. It works by mimicking a hormone that regulates hunger and slows gastric emptying. Liraglutide is used to manage type 2 diabetes and promote weight loss in individuals with obesity or overweight. It helps control blood sugar levels and reduce appetite. Liraglutide injection typically costs between $800 and $1,000 per month without insurance. Prices may vary based on location, pharmacy, and insurance coverage. Disadvantages of liraglutide include potential side effects such as nausea, vomiting, and risk of pancreatitis. It can also be costly and may require regular injections. Individuals eligible for liraglutide include those with type 2 diabetes who need improved blood sugar control and those with obesity or overweight for weight management. Eligibility should be determined by a healthcare provider based on specific health conditions. Liraglutide has been shown to be effective in lowering blood sugar levels in people with type 2 diabetes and achieving significant weight loss in individuals with obesity. Success rates can vary based on individual response and adherence to treatment. Liraglutide is a type of medication you might need to take to help you lose weight. What is liraglutide? Liraglutide belongs to a group of drugs called GLP-1 agonists. There are several different GLP-1 agonists available in the UK. You can take liraglutide it on its own or with other diabetes medications. How does liraglutide work? Liraglutude has the brand name Saxenda, and used to have the brand name Victoza. Saxenda Saxenda is used as a weight loss drug. It helps to reduce appetite, so you feel fuller for longer. It can also reduce the risk of heart disease. Victoza Victoza was used to treat type 2 diabetes. It worked by helping your body to produce more insulin when needed. It also reduced the amount of glucose produced by the body and slowed down how quickly food is digested. Victoza has now been discontinued. How to take liraglutide Liraglutide is an injection that you take once a day. Your healthcare team will give you more information about how to take liraglutide, and how to inject. Always take liraglutide exactly as your healthcare professional has told you. The Patient Information Leaflet inside the box will tell you how to take it but always check with your healthcare professional if you are not sure. Who can take liraglutide? Adults or children over 12 years old can take liraglutide. You might be eligible for this medication if you have have a Body Mass Index, known as BMI, of $35kg/m^2$ or more, you have prediabetes or type 2 diabetes, and you're at high risk of heart problems such as heart attack and stroke. Liraglutide can only be prescribed by weight management services, so you will need to be referred to specialist NHS weight management services by your doctor, or privately through a registered healthcare professional. Guidelines from The National Institute of Health and Care Excellence, or NICE for short, recommend – due to their risk from obesity-related health problems at a lower BMI – that people from Black African, African-Caribbean, Asian, South Asian, Chinese, and Middle Eastern backgrounds receive treatment with liraglutide at a lower BMI. Who can't take liraglutide? Some medications might not be suitable for some people, which might be because of medical conditions or other reasons: Your doctor might tell you to stop taking liraglutide if you develop diabetic ketoacidosis, or DKA; If you have kidney disease you might not be able to take liraglutide, but this will depend on the stage of your kidney disease; If you have severe liver disease you will not be able to take liraglutide; You might need to temporarily stop liraglutide if you're going to have an operation; You should not take liraglutide if you are pregnant of breastfeeding. If you're planning a pregnancy speak with a healthcare professional if you are using this medication. When you start a new medication always check with your healthcare team that it's suitable for you to take. Your prescription You should only be given a prescription for liraglutide following an assessment by your healthcare team to make sure that you meet the criteria and that you'll benefit from its use. This should be an individual assessment that includes how liraglutide will fit into your current treatment plan and considers any diet or activity programme that you are following, as well as the risk of side effects, the dose you'll need, and your personal choices. Your healthcare team should explain your prescription to you but it's important to make sure you ask if you don't feel you know enough. And make sure you talk to your GP or your diabetes team if you struggle to take liraglutide. They might be able to help by giving you a different dose. In England, if you need to take any medication to manage your diabetes, your prescriptions will be free. Ask your healthcare team about a prescription exemption certificate if you don't have one, to make sure you don't get charged for your medication. Prescriptions are already free for everybody in the rest of the UK, so you shouldn't pay for your medication. Liraglutide (Victoza) side effects Side effects from taking liraglutide include: feeling or being sick, diarrhoea, and reduced appetite (which should normally pass over time) risk of low blood sugar risk of high blood sugar. Risk of low blood sugar When taken on its own, liraglutide does not often cause blood sugar levels to become too low. However, hypos are more common when you take liraglutide with other diabetes medications, such as insulin or a sulphonylurea. Your healthcare team may advise reducing the dose of your sulphonylurea or insulin when you start taking liraglutide to reduce the risk of hypos. Risk of high blood sugar If you take liraglutide with insulin and your insulin dose is reduced too quickly it can cause high blood sugar levels or hyperglycaemia, also known as hypers, and there is an increased risk of diabetic ketoacidosis, also called DKA. Your healthcare team should discuss with you the signs and symptoms of DKA. These are not all the side effects. You will find a full list of known side effects in the Patient Information Leaflet. This comes in the medication box. Like all medications, liraglutide can cause side effects. But when side effects are listed as common in the Patient Information Leaflet, it doesn't mean that everyone who takes the medication will get them. The information about side effects is based on the likelihood of people having them. For example, if a side effect is very common then it can affect more than one in ten people, and if a side effect is very rare then it affects fewer than one in 10,000 people. Because medicines can affect people differently, your healthcare team will speak to you about what's best for you and discuss any side effects. Side effects include: It's also important that you take individual advice from your healthcare team before starting liraglutide treatment and report any side effects to your healthcare professionals, if you experience any. You can also report these side effects to the Yellow Card Scheme, which is the government system used for recording side effects with medicines in the UK. More information and support Still have more questions? Or is there anything you're not sure about liraglutide after reading this page? Contact our helpline on 0345 123 2399. You can visit the NHS website for more information on liraglutide. LIRAGLUTIDE (LIR a GLOO tide) treats type 2 diabetes. It may also be used to prevent a stroke or heart attack in people with diabetes. It works by increasing insulin levels in your body, which decreases your blood sugar (glucose). Changes to diet and exercise are often combined with this medication.This medicine may be used for other purposes; ask your health care provider or pharmacist if you have questions.COMMON BRAND NAME(S): VictozaWhat should I tell my care team before I take this medication?They need to know if you have any of these conditions:Endocrine tumors (MEN 2) or if someone in your family had these tumorsGallbladder diseaseHigh cholesterolHistory of pancreatitisKidney disease or if you are on dialysisLiver diseasePrevious swelling of the tongue, face, or lips with difficulty breathing, difficulty swallowing, hoarseness, or tightening of the throatStomach problemsSubstance use disorderThyroid cancer or if someone in your family had thyroid cancerAn unusual or allergic reaction to liraglutide, other medications, foods, dyes, or preservativesPregnant or trying to get pregnantBreast-feedingHow should I use this medication?This medication is for injection under the skin of your upper leg, stomach area, or upper arm. You will be taught how to prepare and give this medication. Use exactly as directed. Take your medication at regular intervals. Do not take it more often than directed.It is important that you put your used needles and syringes in a special sharps container. Do not put them in a trash can. If you do not have a sharps container, call your pharmacist or care team to get one.A special MedGuide will be given to you by the pharmacist with each prescription and refill. Be sure to read this information carefully each time.This medication comes with INSTRUCTIONS FOR USE. Ask your pharmacist for directions on how to use this medication. Read the information carefully. Talk to your pharmacist or care team if you have questions.Talk to your care team regarding the use of this medication in children. While this medication may be prescribed for children as young as 10 years of age, precautions do apply.Overdosage: If you think you have taken too much of this medicine contact a poison control center or emergency room at once.NOTE: This medicine is only for you. Do not share this medicine with others.What if I miss a dose?If you miss a dose, take it as soon as you can. If it is almost time for your next dose, take only that dose. Do not take double or extra doses.What may interact with this medication?Alcohol containing beveragesAntiviral medications for HIV or AIDSAspirin and aspirin-like medicationsBeta-blockers like atenolol, metoprolol, propranololCertain medications for blood pressure, heart disease, irregular heart beatChromiumClonidineDiureticsFemale hormones, such as estrogens or progestins, birth control pillsFenofibrateGemfibrozilGuanethidineIsoniazidLanreotideMale hormones or anabolic steroidsMAOIs like Carbex, Eldepryl, Marplan, Nardil, and ParnateMedications for weight lossMedications for allergies, asthma, cold, or coughMedications for depression, anxiety, or psychotic disturbancesNiacinNicotineNSAIDs, medications for pain and inflammation, like ibuprofen or naproxenOctreotideOther medications for diabetes, like glyburide, glipizide, or glimepiridePasireotidePentamidinePhenytoinProbenecidQuinolone antibiotics such as ciprofloxacin, levofloxacin, ofloxacinReserpineSome herbal dietary supplementsSteroid medications such as prednisone or cortisoneSulfamethoxazole; trimethoprimThyroid hormonesThis list may not describe all possible interactions. Give your health care provider a list of all the medicines, herbs, non-prescription drugs, or dietary supplements you use. Also tell them if you smoke, drink alcohol, or use illegal drugs. Some items may interact with your medicine.What should I watch for while using this medication?Visit your care team for regular checks on your progress.Drink plenty of fluids while taking this medication. Check with your care team if you get an attack of severe diarrhea, nausea, and vomiting. The loss of too much body fluid can make it dangerous for you to take this medication.A test called the HbA1C (A1C) will be monitored. This is a simple blood test. It measures your blood sugar control over the last 2 to 3 months. You will receive this test every 3 to 6 months.Learn how to check your blood sugar. Learn the symptoms of low and high blood sugar and how to manage them.Always carry a quick-source of sugar with you in case you have symptoms of low blood sugar. Examples include hard sugar candy or glucose tablets. Make sure others know that you can choke if you eat or drink when you develop serious symptoms of low blood sugar, such as seizures or unconsciousness. They must get medical help at once.Tell your care team if you have high blood sugar. You might need to change the dose of your medication. If you are sick or exercising more than usual, you might need to change the dose of your medication.Do not skip meals. Ask your care team if you should avoid alcohol. Many nonprescription cough and cold products contain sugar or alcohol. These can affect blood sugar.Pens should never be shared. Even if the needle is changed, sharing may result in passing of viruses like hepatitis or HIV.Wear a medical ID bracelet or chain, and carry a card that describes your disease and details of your medication and dosage times.What side effects may I notice from receiving this medication?Side effects that you should report to your care team as soon as possible:Allergic reactions or angioedema—skin rash, itching, hives, swelling of the face, eyes, lips, tongue, arms, or legs, trouble swallowing or breathingGallbladder problems—severe stomach pain, nausea, vomiting, feverKidney injury—decrease in the amount of urine, swelling of the ankles, hands, or feetPancreatitis—severe stomach pain that spreads to your back or gets worse after eating or when touched, fever, nausea, vomitingThyroid cancer—new mass or lump in the neck, pain or trouble swallowing, trouble breathing, hoarsenessSide effects that usually do not require medical attention (report to your care team if they continue or are bothersome):ConstipationLoss of AppetiteNauseaUpset stomachThis list may not describe all possible side effects. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.Where should I keep my medication?Keep out of the reach of children and pets.Store unopened pen in a refrigerator between 2 and 8 degrees C (36 and 46 degrees F). Do not freeze or use if the medication has been frozen. Protect from light and excessive heat. After you first use the pen, it can be stored at room temperature between 15 and 30 degrees C (59 and 86 degrees F) or in a refrigerator. Throw away your used pen after 30 days or after the expiration date, whichever comes first.Do not store your pen with the needle attached. If the needle is left on, medication may leak from the pen.NOTE: This sheet is a summary. It may not cover all possible information. If you have questions about this medicine, talk to your doctor, pharmacist, or health care provider. Updated January 13, 2025 If you are a consumer or patient please visit this version. HIGHLIGHTS OF PRESCRIBING INFORMATION These highlights do not include all the information needed to use LIRAGLUTIDE INJECTION safely and effectively. See full prescribing information for LIRAGLUTIDE INJECTION.LIRAGLUTIDE injection, for subcutaneous useInitial U.S. Approval: 2010 Liraglutide causes thyroid C-cell tumors at clinically relevant exposures in both genders of rats and mice. It is unknown whether liraglutide injection causes thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans, as the human relevance of liraglutide-induced rodent thyroid C-cell tumors has not been determined (5.1, 13.1). Liraglutide injection is contraindicated in patients with a personal or family history of MTC or in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2). Counsel patients regarding the potential risk of MTC and the symptoms of thyroid tumors (4, 5.1). Warning and Precautions, Pulmonary Aspiration During General Anesthesia or Deep Sedation (5.8)...11/2024 Liraglutide injection is a glucagon-like peptide-1 (GLP-1) receptor agonist indicated: as an adjunct to diet and exercise to improve glycemic control in adults and pediatric patients aged 10 years and older with type 2 diabetes mellitus (1). Limitations of Use: Not for treatment of type 1 diabetes mellitus. Should not be coadministered with other liraglutide-containing products. Adult Patients: Initiate at 0.6 mg injected subcutaneously once daily for one week then increase to 1.2 mg daily. If additional glycemic control is required, increase the dose to 1.8 mg daily after one week of treatment with the 1.2 mg daily dose (2.1). Pediatric Patients: Initiate at 0.6 mg injected subcutaneously once daily for at least one week. If additional glycemic control is required increase the dose to 1.2 mg daily and if additional glycemic control is still required, increase the dose to 1.8 mg daily after at least one week of treatment with the 1.2 mg daily dose (2.1). Inspect visually prior to each injection. Only use if solution is clear, colorless, and contains no particles (2.3). Inject liraglutide injection subcutaneously once-daily at any time of day, independently of meals, in the abdomen, thigh or upper arm (2.3). When using liraglutide injection with insulin, administer as separate injections. Never mix. (2.3). Injection: 6 mg/mL solution in a pre-filled, single-patient-use pen that delivers doses of 0.6 mg, 1.2 mg, or 1.8 mg (3). Patients with a personal or family history of medullary thyroid carcinoma or in patients with Multiple Endocrine Neoplasia syndrome type 2 (4). Patients with a serious hypersensitivity reaction to liraglutide or any of the excipients in liraglutide injection (4). Pancreatitis: Postmarketing reports, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis. Discontinue promptly if pancreatitis is suspected. Do not restart if pancreatitis is confirmed (5.2). Never share a liraglutide injection pen between patients, even if the needle is changed (5.3). Hypoglycemia: Adult patients taking an insulin secretagogue or insulin may have an increased risk of hypoglycemia, including severe hypoglycemia. In pediatric patients 10 years of age and older, the risk of hypoglycemia was higher with liraglutide injection regardless of insulin and/or metformin use. Reduction in the dose of insulin secretagogues or insulin may be necessary (5.4). Acute Kidney Injury: Postmarketing, usually in association with nausea, vomiting, diarrhea, or dehydration which may sometimes require hemodialysis. Use caution when initiating or escalating doses of liraglutide injection in patients with renal impairment (5.5). Hypersensitivity Reactions: Postmarketing reports of serious hypersensitivity reactions (e.g., anaphylactic reactions and angioedema). Discontinue liraglutide injection and promptly seek medical advice (5.6). Acute Gallbladder Disease: If cholelithiasis or cholecystitis are suspected, gallbladder studies are indicated (5.7). Pulmonary Aspiration During General Anesthesia or Deep Sedation: Has been reported in patients receiving GLP-1 receptor agonists undergoing elective surgeries or procedures. Instruct patients to inform healthcare providers of any planned surgeries or procedures (5.8). Most common adverse reactions (incidence ≥5%) in clinical trials are nausea, diarrhea, vomiting, decreased appetite, dyspepsia, constipation (6.1). Immunogenicity-related events, including urticaria, were more common among liraglutide injection-treated patients (0.8%) than among comparator-treated patients (0.4%) in clinical trials (12.6). To report SUSPECTED ADVERSE REACTIONS, contact Hikma Pharmaceuticals USA Inc. at 1-877-845-0689 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch. Effects of delayed gastric emptying on oral medications: Liraglutide injection delays gastric emptying and may impact absorption of concomitantly administered oral medications (7). Pregnancy: Liraglutide injection should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus (8.1). See 17 for PATIENT COUNSELING INFORMATION and Medication Guide. Revised: 1/2025 Table of Contents BOXED WARNING (What is this?) WARNING: RISK OF THYROID C-CELL TUMORS Liraglutide causes dose-dependent and treatment-duration-dependent thyroid C-cell tumors at clinically relevant exposures in both genders of rats and mice. It is unknown whether liraglutide injection causes thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans, as the human relevance of liraglutide-induced rodent thyroid C-cell tumors has not been determined [see Warnings and Precautions (5.1) and Nonclinical Toxicology (13.1)]. Liraglutide injection is contraindicated in patients with a personal or family history of MTC and in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2). Counsel patients regarding the potential risk for MTC with the use of liraglutide injection and inform them of symptoms of thyroid tumors (e.g., a mass in the neck, dysphagia, dyspnea, persistent hoarseness). Routine monitoring of serum calcitonin or using thyroid ultrasound is of uncertain value for early detection of MTC in patients treated with liraglutide injection [see Contraindications (4) and Warnings and Precautions (5.1)]. 1 INDICATIONS AND USAGE Liraglutide injection is indicated: as an adjunct to diet and exercise to improve glycemic control in adults and pediatric patients aged 10 years and older with type 2 diabetes mellitus Limitations of Use: Liraglutide injection should not be used in patients with type 1 diabetes mellitus. Liraglutide injection contains liraglutide and should not be coadministered with other liraglutide-containing products. 2 DOSAGE AND ADMINISTRATION 2.1 Recommended Dosage Adult Patients The recommended starting dosage of liraglutide injection is 0.6 mg injected subcutaneously once daily for one week. The 0.6 mg once daily dosage is intended to reduce gastrointestinal symptoms [see Adverse Reactions (6.1)] during initial titration and is not effective for glycemic control in adults. After one week at the 0.6 mg once daily dosage, increase the dosage to 1.2 mg injected subcutaneously once daily. If additional glycemic control is required, increase the dosage to the maximum recommended dosage of 1.8 mg injected subcutaneously once daily after at least one week of treatment with the 1.2 mg once daily dosage. Pediatric Patients Aged 10 Years and Older The recommended starting dosage of liraglutide injection is 0.6 mg injected subcutaneously once daily. If additional glycemic control is required, increase the dosage in 0.6 mg increments after at least one week on the current dosage. The maximum recommended dosage is 1.8 mg injected subcutaneously once daily. 2.2 Recommendations Regarding Missed Dose Instruct patients who miss a dose of liraglutide injection to resume the once -daily dosage regimen as prescribed with the next scheduled dose. Do not administer an extra dose or increase the dose to make up for the missed dose. If more than 3 days have elapsed since the last liraglutide injection dose, reinitiate liraglutide injection at 0.6 mg once daily to mitigate any gastrointestinal symptoms associated with reinitiation of treatment. Upon reinitiation, liraglutide injection should be titrated at the discretion of the healthcare provider. 2.3 Important Administration Instructions Inspect visually prior to each injection. Only use if solution is clear, colorless, and contains no particles. Inject liraglutide injection subcutaneously once daily at any time of day, independently of meals. Inject liraglutide injection subcutaneously in the abdomen, thigh or upper arm. No dosage adjustment is needed if changing the injection site and/or timing. Rotate injection sites within the same region in order to reduce the risk of cutaneous amyloidosis [see Adverse Reactions (6.2)]. When using liraglutide injection with insulin, administer as separate injections. Never mix. It is acceptable to inject liraglutide injection and insulin in the same body region but the injections should not be adjacent to each other. 3 DOSAGE FORMS AND STRENGTHS Injection: 18 mg/3 mL (6 mg/mL) clear, colorless solution in a pre-filled, single-patient-use pen that delivers doses of 0.6 mg, 1.2 mg, or 1.8 mg. 4 CONTRAINDICATIONS Liraglutide injection is contraindicated in patients with a: personal or family history of medullary thyroid carcinoma (MTC) or in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2) [see Warnings and Precautions (5.1)]. serious hypersensitivity reaction to liraglutide or to any of the excipients in liraglutide injection. Serious hypersensitivity reactions including anaphylactic reactions and angioedema have been reported with liraglutide injection [see Warnings and Precautions (5.6)]. 5 WARNINGS AND PRECAUTIONS 5.1 Risk of Thyroid C-cell Tumors Liraglutide causes dose-dependent and treatment-duration-dependent thyroid C-cell tumors (adenomas and/or carcinomas) at clinically relevant exposures in both genders of rats and mice [see Nonclinical Toxicology (13.1)]. Malignant thyroid C-cell carcinomas were detected in rats and mice. It is unknown whether liraglutide injection will cause thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans, as the human relevance of liraglutide-induced rodent thyroid C-cell tumors has not been determined. Cases of MTC in patients treated with liraglutide injection have been reported in the postmarketing period; the data in these reports are insufficient to establish or exclude a causal relationship between MTC and liraglutide injection use in humans. Liraglutide injection is contraindicated in patients with a personal or family history of MTC or in patients with MEN 2. Counsel patients regarding the potential risk for MTC with the use of liraglutide injection and inform them of symptoms of thyroid tumors (e.g., a mass in the neck, dysphagia, dyspnea, persistent hoarseness). Routine monitoring of serum calcitonin or using thyroid ultrasound is of uncertain value for early detection of MTC in patients treated with liraglutide injection. Such monitoring may increase the risk of unnecessary procedures, due to low test specificity for serum calcitonin and a high background incidence of thyroid disease. Significantly elevated serum calcitonin may indicate MTC and patients with MTC usually have calcitonin values >50 ng/L. If serum calcitonin is measured and found to be elevated, the patient should be further evaluated. Patients with thyroid nodules noted on physical examination or neck imaging should also be further evaluated. 5.2 Pancreatitis Based on spontaneous postmarketing reports, acute pancreatitis, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis, has been observed in patients treated with liraglutide injection. After initiation of liraglutide injection, observe patients carefully for signs and symptoms of pancreatitis (including persistent severe abdominal pain, sometimes radiating to the back and which may or may not be accompanied by vomiting). If pancreatitis is suspected, liraglutide injection should promptly be discontinued and appropriate management should be initiated. If pancreatitis is confirmed, liraglutide injection should not be restarted. In glycemic control trials of liraglutide injection, there have been 13 cases of pancreatitis among liraglutide injection-treated patients and 1 case in a comparator (glimepiride) treated patient (2.7 vs. 0.5 cases per 1,000 patient-years). Nine of the 13 cases with liraglutide injection were reported as acute pancreatitis and four were reported as chronic pancreatitis. In one case in a liraglutide injection-treated patient, pancreatitis, with necrosis, was observed and led to death; however clinical causality could not be established. Some patients had other risk factors for pancreatitis, such as a history of cholelithiasis or alcohol abuse. Liraglutide injection has been studied in a limited number of patients with a history of pancreatitis. It is unknown if patients with a history of pancreatitis are at higher risk for development of pancreatitis on liraglutide injection. 5.3 Never Share a Liraglutide Injection Pen Between Patients Liraglutide injection pens must never be shared between patients, even if the needle is changed. Pen-sharing poses a risk for transmission of blood-borne pathogens. 5.4 Hypoglycemia Adult patients receiving liraglutide injection in combination with an insulin secretagogue (e.g., sulfonylurea) or insulin may have an increased risk of hypoglycemia, including severe hypoglycemia. In pediatric patients 10 years of age and older, the risk of hypoglycemia was higher with liraglutide injection regardless of insulin and/or metformin use. [see Adverse Reactions (6.1), Drug Interactions (7.2)]. The risk of hypoglycemia may be lowered by a reduction in the dose of sulfonylurea (or other concomitantly administered insulin secretagogues) or insulin. Inform patients using these concomitant medications and pediatric patients of the risk of hypoglycemia and educate them on the signs and symptoms of hypoglycemia. 5.5 Acute Kidney Injury Liraglutide injection has not been found to be directly nephrotoxic in animal studies or clinical trials. There have been postmarketing reports of acute renal failure and worsening of chronic renal failure, which may sometimes require hemodialysis in liraglutide injection-treated patients [see Adverse Reactions (6.2)]. Some of these events were reported in patients without known underlying renal disease. A majority of the reported events occurred in patients who had experienced nausea, vomiting, diarrhea, or dehydration [see Adverse Reactions (6.1)]. Some of the reported events occurred in patients receiving one or more medications known to affect renal function or hydration status. Altered renal function has been reversed in many of the reported cases with supportive treatment and discontinuation of potentially causative agents, including liraglutide injection. Use caution when initiating or escalating doses of liraglutide injection in patients with renal impairment [see Use in Specific Populations (8.6)]. 5.6 Hypersensitivity Reactions There have been postmarketing reports of serious hypersensitivity reactions (e.g., anaphylactic reactions and angioedema) in patients treated with liraglutide injection [see Adverse Reactions (6.2)]. If a hypersensitivity reaction occurs, discontinue liraglutide injection; treat promptly per standard of care, and monitor until signs and symptoms resolve. Anaphylaxis and angioedema have been reported with other GLP-1 receptor agonists. Use caution in a patient with a history of anaphylaxis or angioedema with another GLP-receptor agonist because it is unknown whether such patients will be predisposed to these reactions with liraglutide injection. Liraglutide injection is contraindicated in patients who have had a serious hypersensitivity reaction to liraglutide or any of the excipients in liraglutide injection [see Contraindications (4)]. 5.7 Acute Gallbladder Disease Acute events of gallbladder disease such as cholelithiasis or cholecystitis have been reported in GLP-1 receptor agonist trials and postmarketing. If cholelithiasis is suspected, gallbladder studies and appropriate clinical follow-up are indicated [see Adverse Reactions (6.1)]. 5.8 Pulmonary Aspiration During General Anesthesia or Deep Sedation Liraglutide injection delays gastric emptying [see Clinical Pharmacology (12.2)]. There have been rare postmarketing reports of pulmonary aspiration in patients receiving GLP-1 receptor agonists undergoing elective surgeries or procedures requiring general anesthesia or deep sedation who had residual gastric contents despite reported adherence to preoperative fasting recommendations. Available data are insufficient to inform recommendations to mitigate the risk of pulmonary aspiration during general anesthesia or deep sedation in patients taking liraglutide injection, including whether modifying preoperative fasting recommendations or temporarily discontinuing liraglutide injection could reduce the incidence of retained gastric contents. Instruct patients to inform healthcare providers prior to any planned surgeries or procedures if they are taking liraglutide injection. 6 ADVERSE REACTIONS The following serious adverse reactions are described below or elsewhere in the prescribing information: Risk of Thyroid C-cell Tumors [see Warnings and Precautions (5.1)] Pancreatitis [see Warnings and Precautions (5.2)] Hypoglycemia [see Warnings and Precautions (5.4)] Acute Kidney Injury [see Warnings and Precautions (5.5)] Hypersensitivity Reactions [see Warnings and Precautions (5.6)] Acute Gallbladder Disease [see Warnings and Precautions (5.7)] Pulmonary Aspiration During General Anesthesia or Deep Sedation [see Warnings and Precautions (5.8)] 6.1 Clinical Trials Experience Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. Common Adverse Reactions The safety of liraglutide injection in patients with type 2 diabetes mellitus was evaluated in 5 glycemic control, placebo-controlled trials in adults and one trial of 52 weeks duration in pediatric patients 10 years of age and older [see Clinical Studies (14.1)]. The data in Table 1 reflect exposure of 1,673 adult patients to liraglutide injection and a mean duration of exposure to liraglutide injection of 37.3 weeks. The mean age of adult patients was 58 years, 4% were 75 years or older and 54% were male. The population was 79% White, 6% Black or African American, 13% Asian; 4% were of Hispanic or Latino ethnicity. At baseline the population had diabetes for an average of 9 years and a mean HbA1c of 8.4%. Baseline estimated renal function was normal or mildly impaired in 88% and moderately impaired in 12% of the pooled population. Table 1 shows common adverse reactions in adults, excluding hypoglycemia, associated with the use of liraglutide injection for the treatment of type 2 diabetes mellitus. These adverse reactions occurred more commonly on liraglutide injection than on placebo and occurred in at least 5% of patients treated with liraglutide injection. Overall, the type, and severity of adverse reactions in pediatric patients 10 years of age and older and above were comparable to that observed in the adult population. Table 1 Adverse reactions reported in ≥ 5% of Adult Patients Treated with Liraglutide Injection for Type 2 Diabetes Mellitus Cumulative proportions were calculated combining studies using Cochran-Mantel-Haenszel weights. In an analysis of placebo- and active-controlled trials, the types and frequency of common adverse reactions, excluding hypoglycemia, were similar to those listed in Table 1. Other Adverse Reactions Gastrointestinal Adverse Reactions In the pool of 5 glycemic control, placebo-controlled adult clinical trials, withdrawals due to gastrointestinal adverse reactions, occurred in 4.3% of liraglutide injection-treated patients and 0.5% of placebo-treated patients. Withdrawal due to gastrointestinal adverse events mainly occurred during the first 2 to 3 months of the trials. Injection site reactions Injection site reactions (e.g., injection site rash, erythema) were reported in approximately 2% of liraglutide injection-treated adult patients in the five double-blind, glycemic control trials of at least 26 weeks duration. Less than 0.2% of liraglutide injection-treated patients discontinued due to injection site reactions. Hypoglycemia In 5 adult glycemic control, placebo-controlled clinical trials of at least 26 weeks duration, hypoglycemia requiring the assistance of another person for treatment occurred in 8 liraglutide injection-treated patients (7.5 events per 1,000 patient-years). Of these 8 liraglutide injection-treated patients, 7 patients were concomitantly using a sulfonylurea. "Patient not able to self-treat" is defined as an event requiring the assistance of another person for treatment. In a 26-week placebo-controlled clinical trial in pediatric patients 10 years of age and older with a 26-week open-label extension, 21.2% of liraglutide injection-treated patients (mean age 14.6 years) with type 2 diabetes mellitus, had hypoglycemia with a blood glucose 10. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively. Clinical Considerations Disease-associated maternal and/or embryo/fetal risk Poorly controlled diabetes in pregnancy increases the maternal risk for diabetic ketoacidosis, pre-eclampsia, spontaneous abortions, preterm delivery, and delivery complications. Poorly controlled diabetes increases the fetal risk for major birth defects, still birth, and macrosomia related morbidity. Animal Data Female rats given subcutaneous doses of 0.1, 0.25 and 1.0 mg/kg/day liraglutide beginning 2 weeks before mating through gestation day 17 had estimated systemic exposures 0.8-, 3-, and 11-times the human exposure at the MRHD based on plasma AUC comparison. The number of early embryonic deaths in the 1 mg/kg/day group increased slightly. Fetal abnormalities and variations in kidneys and blood vessels, irregular ossification of the skull, and a more complete state of ossification occurred at all doses. Mottled liver and minimally kinked ribs occurred at the highest dose. The incidence of fetal malformations in liraglutide-treated groups exceeding concurrent and historical controls were misshapen oropharynx and/or narrowed opening into larynx at 0.1 mg/kg/day and umbilical hernia at 0.1 and 0.25 mg/kg/day. Pregnant rabbits given subcutaneous doses of 0.01, 0.025 and 0.05 mg/kg/day liraglutide from gestation day 6 through day 18 inclusive, had estimated systemic exposures less than the human exposure at the MRHD of 1.8 mg/day at all doses, based on plasma AUC. Liraglutide decreased fetal weight and dose-dependently increased the incidence of total major fetal abnormalities at all doses. The incidence of malformations exceeded concurrent and historical controls at 0.01 mg/kg/day (kidneys, scapula), ≥ 0.01 mg/kg/day (eyes, forelimb), 0.025 mg/kg/day (brain, tail and sacral vertebrae, major blood vessels and heart, umbilicus), ≥ 0.025 mg/kg/day (sternum) and at 0.05 mg/kg/day (parietal bones, major blood vessels). Irregular ossification and/or skeletal abnormalities occurred in the skull and jaw, vertebrae and ribs, sternum, pelvis, tail, and scapula; and dose-dependent minor skeletal variations were observed. Visceral abnormalities occurred in blood vessels, lung, liver, and esophagus. Bilobed or bifurcated gallbladder was seen in all treatment groups, but not in the control group. In pregnant female rats given subcutaneous doses of 0.1, 0.25 and 1.0 mg/kg/day liraglutide from gestation day 6 through weaning or termination of nursing on lactation day 24, estimated systemic exposures were 0.8-, 3-, and 11-times human exposure at the MRHD of 1.8 mg/day, based on plasma AUC. A slight delay in parturition was observed in the majority of treated rats. Group mean body weight of neonatal rats from liraglutide-treated dams was lower than neonatal rats from control group dams. Bloody scabs and agitated behavior occurred in male rats descended from dams treated with 1 mg/kg/day liraglutide. Group mean body weight from birth to postpartum day 14 trended lower in F2 generation rats descended from liraglutide-treated rats compared to F2 generation rats descended from controls, but differences did not reach statistical significance for any group. 8.2 Lactation Risk Summary There are no data on the presence of liraglutide injection in human milk, the effects on the breastfed infant, or the effects on milk production. Liraglutide was present in milk of lactating rats [see Data]. Developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for liraglutide injection and any potential adverse effects on the breastfed infant from liraglutide injection or from the underlying maternal condition. Data In lactating rats, liraglutide was present unchanged in milk at concentrations approximately 50% of maternal plasma concentrations. 8.4 Pediatric Use The safety and effectiveness of liraglutide injection as an adjunct to diet and exercise to improve glycemic control in type 2 diabetes mellitus have been established in pediatric patients 10 years of age and older. Use of liraglutide injection for this indication is supported by a 26-week placebo-controlled clinical trial and a 26-week open-label extension in 134 pediatric patients 10 to 17 years of age with type 2 diabetes mellitus, a pediatric pharmacokinetic study, and studies in adults with type 2 diabetes mellitus [see Clinical Pharmacology (12.3) and Clinical Studies (14.1,14.2)]. The risk of hypoglycemia was higher with liraglutide injection in pediatric patients regardless of insulin and/or metformin use [see Adverse Reactions (6.1)]. The safety and effectiveness of liraglutide injection have not been established in pediatric patients less than 10 years of age. 8.5 Geriatric Use In the liraglutide injection treatment arms of the glycemic control trials, a total of 832 (19.3%) of the patients were 65 to 74 years of age and 145 (3.4%) were 75 years of age and over [see Clinical Studies (14.1)]. No overall differences in safety or effectiveness for liraglutide injection have been observed between patients 65 years of age and older and younger patients. 8.6 Renal Impairment No dose adjustment of liraglutide injection is recommended for patients with renal impairment [see Clinical Pharmacology (12.3)]. The safety and efficacy of liraglutide injection was evaluated in a 26-week clinical study that included patients with moderate renal impairment (eGFR 30 to 60 mL/min/1.73m2) [see Clinical Studies (14.1)]. There is limited experience with liraglutide injection in patients with end stage renal disease. There have been postmarketing reports of acute renal failure and worsening of chronic renal failure, which may sometimes require hemodialysis [see Warnings and Precautions (5.5) and Adverse Reactions (6.2)]. Use caution in patients who experience dehydration. 8.7 Hepatic Impairment There is limited experience in patients with mild, moderate or severe hepatic impairment. Therefore, liraglutide injection should be used with caution in this patient population. No dose adjustment of liraglutide injection is recommended for patients with hepatic impairment [see Clinical Pharmacology (12.3)]. 8.8 Gastroparesis Liraglutide injection slows gastric emptying. Liraglutide injection has not been studied in patients with pre-existing gastroparesis. 10 OVERDOSAGE Overdoses have been reported in clinical trials and post-marketing use of liraglutide injection. Observed effects have included severe nausea, severe vomiting, and severe hypoglycemia. In the event of overdosage, appropriate supportive treatment should be initiated according to the patient's clinical signs and symptoms. 11 DESCRIPTION Liraglutide Injection contains liraglutide, an analog of human GLP-1 and acts as a GLP-1 receptor agonist. Liraglutide Injection contains chemically synthesized Liraglutide that has been engineered to be 97% homologous to native human GLP-1 by substituting arginine for lysine at position 34. Liraglutide is made by attaching a C-16 fatty acid (palmitic acid) with a glutamic acid spacer on the remaining lysine residue at position 26 of the peptide precursor. The molecular formula of liraglutide is $C_{172}H_{265}N_{43}O_{51}$ and the molecular weight is 3751.2 Daltons. The structural formula (Figure 1) is: Figure 1 Structural Formula of liraglutide Liraglutide Injection is a sterile, aqueous, clear, colorless or almost colorless solution for subcutaneous use. Each 1 mL of Liraglutide Injection solution contains 6 mg of liraglutide and the following inactive ingredients: disodium phosphate dihydrate, 1.42 mg; propylene glycol, 14 mg; phenol, 5.5 mg; and water for injection. Liraglutide Injection has a pH of approximately 8.15, hydrochloric acid or sodium hydroxide may be added to adjust pH. Each pre-filled pen contains a 3 mL solution of Liraglutide Injection equivalent to 18 mg liraglutide (free-base, anhydrous). 12 CLINICAL PHARMACOLOGY 12.1 Mechanism of Action Liraglutide is an acylated human Glucagon-Like Peptide-1 (GLP-1) receptor agonist with 97% amino acid sequence homology to endogenous human GLP-1(7-37). GLP-1(7-37) represents 98%). Elimination The mean apparent clearance following subcutaneous administration of a single dose of liraglutide is approximately 1.2 L/h with an elimination half-life of approximately 13 hours. Metabolism During the initial 24 hours following administration of a single [3H]-liraglutide dose to healthy subjects, the major component in plasma was intact liraglutide. Liraglutide is endogenously metabolized in a similar manner to large proteins without a specific organ as a major route of elimination. Excretion Following a [3H]-liraglutide dose, intact liraglutide was not detected in urine or feces. Only a minor part of the administered radioactivity was excreted as liraglutide-related metabolites in urine or feces (6% and 5%, respectively). The majority of urine and feces radioactivity was excreted during the first 6 to 8 days. Specific Populations Geriatric Patients Age had no effect on the pharmacokinetics of liraglutide injection based on a pharmacokinetic study in healthy elderly subjects (65 to 83 years) and population pharmacokinetic analyses of patients 18 to 80 years of age [see Use in Specific Populations (8.5)]. Pediatric Patients A population pharmacokinetic analysis was conducted for liraglutide injection using data from 72 pediatric patients (10 to 17 years of age) with type 2 diabetes mellitus. The pharmacokinetic profile of liraglutide injection in the pediatric patients was consistent with that in adults. Male and Female Patients Based on the results of population pharmacokinetic analyses, females have 25% lower weight-adjusted clearance of liraglutide injection compared to males. Race or Ethnic Groups Race and ethnicity had no effect on the pharmacokinetics of liraglutide injection based on the results of population pharmacokinetic analyses that included White, Black or African American, Asian and Hispanic or Latino/Non-Hispanic or Latino subjects. Body Weight Body weight significantly affects the pharmacokinetics of liraglutide injection based on results of population pharmacokinetic analyses. The exposure of liraglutide decreases with an increase in baseline body weight. However, the 1.2 mg and 1.8 mg daily doses of liraglutide injection provided adequate systemic exposures over the body weight range of 40 to 160 kg evaluated in the clinical trials. Liraglutide was not studied in patients with body weight >160 kg. Patients with Renal Impairment The single-dose pharmacokinetics of liraglutide injection were evaluated in patients with varying degrees of renal impairment. Patients with mild (estimated creatinine clearance 50 to 80 mL/min) to severe (estimated creatinine clearance 9) hepatic impairment were included in the trial. Compared to healthy subjects, liraglutide AUC in patients with mild, moderate and severe hepatic impairment was on average 11%, 14% and 42% lower, respectively [see Use in Specific Populations (8.7)]. Drug Interactions Studies In vitro assessment of drug-drug interactions Liraglutide injection has low potential for pharmacokinetic drug-drug interactions related to cytochrome P450 (CYP) and plasma protein binding. In vivo assessment of drug-drug interactions The drug-drug interaction studies were performed at steady state with liraglutide injection 1.8 mg/day. Before administration of concomitant treatment, subjects underwent a 0.6 mg weekly dose increase to reach the maximum dose of 1.8 mg/day. Administration of the interacting drugs was timed so that Cmax of liraglutide injection (8 to 12 h) would coincide with the absorption peak of the co-administered drugs. Digoxin A single dose of digoxin 1 mg was administered 7 hours after the dose of liraglutide injection at steady state. The concomitant administration with liraglutide injection resulted in a reduction of digoxin AUC by 16%; Cmax decreased by 31%. Digoxin median time to maximal concentration (Tmax) was delayed from 1 h to 1.5 h. Lisinopril A single dose of lisinopril 20 mg was administered 5 minutes after the dose of liraglutide injection at steady state. The co-administration with liraglutide injection resulted in a reduction of lisinopril AUC by 15%; Cmax decreased by 27%. Lisinopril median Tmax was delayed from 6 h to 8 h with Liraglutide Injection. Atorvastatin Liraglutide injection did not change the overall exposure (AUC) of atorvastatin following a single dose of atorvastatin 40 mg, administered 5 hours after the dose of liraglutide injection at steady state. Atorvastatin Cmax was decreased by 38% and median Tmax was delayed from 1 h to 3 h with liraglutide injection. Acetaminophen Liraglutide injection did not change the overall exposure (AUC) of acetaminophen following a single dose of acetaminophen 1,000 mg, administered 8 hours after the dose of liraglutide injection at steady state. Acetaminophen Cmax was decreased by 31% and median Tmax was delayed up to 15 minutes. Griseofulvin Liraglutide injection did not change the overall exposure (AUC) of griseofulvin following co-administration of a single dose of griseofulvin 500 mg with liraglutide injection at steady state. Griseofulvin Cmax increased by 37% while median Tmax did not change. Oral Contraceptives A single dose of an oral contraceptive combination product containing 0.03 mg ethinylestradiol and 0.15 mg levonorgestrel was administered under fed conditions and 7 hours after the dose of liraglutide injection at steady state. Liraglutide injection lowered ethinylestradiol and levonorgestrel Cmax by 12% and 13%, respectively. There was no effect of liraglutide injection on the overall exposure (AUC) of ethinylestradiol. Liraglutide injection increased the levonorgestrel $AUC_{0-\infty}$ by 18%. Liraglutide injection delayed Tmax for both ethinylestradiol and levonorgestrel by 1.5 h. Insulin Detemir No pharmacokinetic interaction was observed between liraglutide injection and insulin detemir when separate subcutaneous injections of insulin detemir 0.5 Unit/kg (single-dose) and liraglutide injection 1.8 mg (steady state) were administered in patients with type 2 diabetes mellitus. 12.6 Immunogenicity The observed incidence of anti-drug antibodies is highly dependent on the sensitivity and specificity of the assay. Differences in assay methods preclude meaningful comparisons of the incidence of anti-drug antibodies in the studies described below with the incidence of anti-drug antibodies in other studies, including those with liraglutide injection or other liraglutide products. A subset of liraglutide injection-treated patients (1,104 of 2,501, 44%) in five adult double-blind clinical trials of 26 weeks duration or longer were tested for the presence of anti-liraglutide antibodies at the end of treatment [see Clinical Studies (14.1)] and 102/1,104 (9%) of liraglutide injection-treated patients developed anti-liraglutide antibodies. Of these 102 liraglutide injection-treated patients, 56 (5%) patients developed antibodies that cross-reacted with native GLP-1. These cross-reacting antibodies were not tested for neutralizing effect against native GLP-1, and thus the potential for clinically significant neutralization of native GLP-1 was not assessed. Antibodies that had a neutralizing effect on liraglutide in an in vitro assay occurred in 12 (1%) of the liraglutide injection-treated patients. There was no identified clinically significant effect of anti-liraglutide antibodies on effectiveness of liraglutide injection. In five double-blind adult glycemic control trials of liraglutide injection, events from a composite of adverse events potentially related to

immunogenicity (e.g., urticaria, angioedema) occurred among 0.8% of liraglutide injection-treated patients and among 0.4% of comparator-treated patients. Urticaria accounted for approximately one-half of the events in this composite for liraglutide injection-treated patients. Patients who developed anti-liraglutide antibodies were not more likely to develop events from the immunogenicity events composite than were patients who did not develop anti-liraglutide antibodies. In a clinical trial with pediatric patients aged 10 years and older [see Clinical Studies (14.2)], anti-liraglutide antibodies were detected in 1 (2%) liraglutide injection-treated patient at week 26 and 5 (9%) liraglutide injection-treated patients at week 53. None of the 5 patients had antibodies cross reactive to native GLP-1 or had neutralizing antibodies. 13 NONCLINICAL TOXICOLOGY 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility A 104-week carcinogenicity study was conducted in male and female CD-1 mice at doses of 0.03, 0.2, 1.0, and 3.0 mg/kg/day liraglutide administered by bolus subcutaneous injection yielding systemic exposures 0.2-, 2-, 10- and 45-times the human exposure, respectively, at the MRHD of 1.8 mg/day based on plasma AUC comparison. A dose-related increase in benign thyroid C-cell adenomas was seen in the 1.0 and the 3.0 mg/kg/day groups with incidences of 13% and 19% in males and 6% and 20% in females, respectively. C-cell adenomas did not occur in control groups or 0.03 and 0.2 mg/kg/day groups. Treatment-related malignant C-cell carcinomas occurred in 3% of females in the 3.0 mg/kg/day group. Thyroid C-cell tumors are rare findings during carcinogenicity testing in mice. A treatment-related increase in fibrosarcomas was seen on the dorsal skin and subcutis, the body surface used for drug injection, in males in the 3 mg/kg/day group. These fibrosarcomas were attributed to the high local concentration of drug near the injection site. The liraglutide concentration in the clinical formulation (6 mg/mL) is 10-times higher than the concentration in the formulation used to administer 3 mg/kg/day liraglutide to mice in the carcinogenicity study (0.6 mg/mL). A 104-week carcinogenicity study was conducted in male and female Sprague Dawley rats at doses of 0.075, 0.25 and 0.75 mg/kg/day liraglutide administered by bolus subcutaneous injection with exposures 0.5-, 2- and 8-times the human exposure, respectively, resulting from the MRHD based on plasma AUC comparison. A treatment-related increase in benign thyroid C-cell adenomas was seen in males in 0.25 and 0.75 mg/kg/day liraglutide groups with incidences of 12%, 16%, 42%, and 46% and in all female liraglutide-treated groups with incidences of 10%, 27%, 33%, and 56% in 0 (control), 0.075, 0.25, and 0.75 mg/kg/day groups, respectively. A treatment-related increase in malignant thyroid C-cell carcinomas was observed in all male liraglutide-treated groups with incidences of 2%, 8%, 6%, and 14% and in females at 0.25 and 0.75 mg/kg/day with incidences of 0%, 0%, 4%, and 6% in 0 (control), 0.075, 0.25, and 0.75 mg/kg/day groups, respectively. Thyroid C-cell carcinomas are rare findings during carcinogenicity testing in rats. Studies in mice demonstrated that liraglutide-induced C-cell proliferation was dependent on the GLP-1 receptor and that liraglutide did not cause activation of the REarranged during Transfection (RET) proto-oncogene in thyroid C-cells. Human relevance of thyroid C-cell tumors in mice and rats is unknown and has not been determined by clinical studies or nonclinical studies [see Boxed Warning and Warnings and Precautions (5.1)]. Liraglutide was negative with and without metabolic activation in the Ames test for mutagenicity and in a human peripheral blood lymphocyte chromosome aberration test for clastogenicity. Liraglutide was negative in repeat-dose in vivo micronucleus tests in rats. In rat fertility studies using subcutaneous doses of 0.1, 0.25 and 1.0 mg/kg/day liraglutide, males were treated for 4 weeks prior to and throughout mating and females were treated 2 weeks prior to and throughout mating until gestation day 17. No direct adverse effects on male fertility was observed at doses up to 1.0 mg/kg/day, a high dose yielding an estimated systemic exposure 11- times the human exposure at the MRHD, based on plasma AUC. In female rats, an increase in early embryonic deaths occurred at 1.0 mg/kg/day. Reduced body weight gain and food consumption were observed in females at the 1.0 mg/kg/day dose. 14 CLINICAL STUDIES 14.1 Glycemic Control Trials in Adults with Type 2 Diabetes Mellitus In glycemic control trials in adults, liraglutide injection has been studied as monotherapy and in combination with one or two oral anti-diabetic medications or basal insulin. In each of the placebo controlled trials, treatment with liraglutide injection produced clinically and statistically significant improvements in hemoglobin A1c and fasting plasma glucose (FPG) compared to placebo. All liraglutide injection-treated patients started at 0.6 mg/day. The dose was increased in weekly intervals by 0.6 mg to reach 1.2 mg or 1.8 mg for patients randomized to these higher doses. Liraglutide injection 0.6 mg is not effective for glycemic control and is intended only as a starting dose to reduce gastrointestinal intolerance [see Dosage and Administration (2)]. Monotherapy In this 52-week trial, 746 adult patients with type 2 diabetes mellitus were randomized to liraglutide injection 1.2 mg, liraglutide injection 1.8 mg, or glimepiride 8 mg. Patients who were randomized to glimepiride were initially treated with 2 mg daily for two weeks, increasing to 4 mg daily for another two weeks, and finally increasing to 8 mg daily. Treatment with liraglutide injection 1.8 mg and 1.2 mg resulted in a statistically significant reduction in HbA1c compared to glimepiride (Table 3). The percentage of patients who discontinued due to ineffective therapy was 3.6% in the liraglutide injection 1.8 mg treatment group, 6.0% in the liraglutide injection 1.2 mg treatment group, and 10.1% in the glimepiride-treatment group. The mean age of participants was 53 years, and the mean duration of diabetes was 5 years. Participants were 49.7% male, 77.5% White, 12.6% Black or African American and 35.0% of Hispanic or Latino ethnicity. The mean BMI was 33.1 kg/m2. Table 3 Results of a 52-week Monotherapy Trial in Adults with Type 2 Diabetes Mellitusa aIntent-to-treat population using last observation on study bLeast squares mean adjusted for baseline value *p-value