Type 2 Diabetes Medications:
Recent Updates and Focus on Injectable Options
October 10, 2018

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Disclosure

- We have nothing to disclose.

Objectives

1. Discuss new products introduced in the last 18 months.
2. List two different FDA safety communications for SGLT-2 inhibitors (canagliflozin, dapagliflozin, empagliflozin, and ertugliflozin).
3. Compare and contrast the different GLP-1 agonists.
4. Discuss concentrated insulin products.

New Products Update

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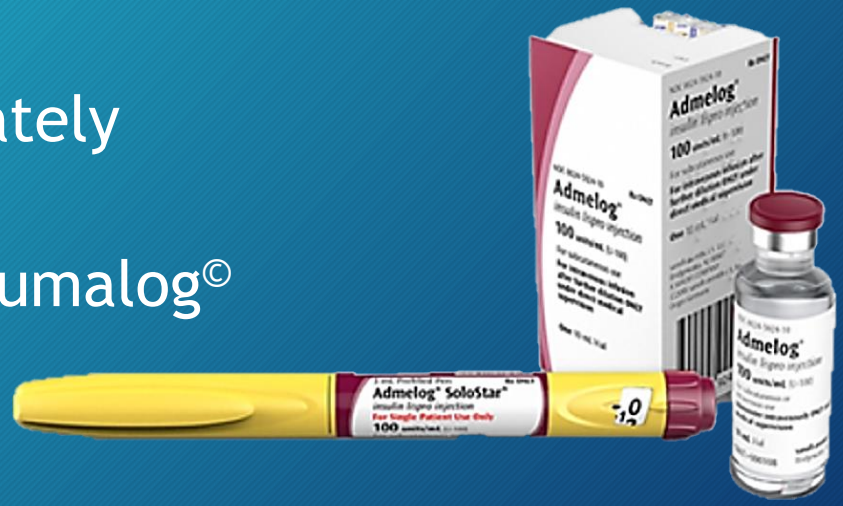
New product: semaglutide (Ozempic©)

- GLP-1 receptor antagonist
- Administration: once-weekly
  - Dosing: 0.25 mg subcutaneously once weekly for 4 weeks, then increase to 0.5 mg once weekly for at least 4 weeks. May titrate to 1 mg once weekly, if needed.
- Adverse effects:
  - Nausea: 16-20%
  - Diarrhea: 9%
  - Vomiting: 5-9%
  - Abdominal pain: 6-7%

Lexi-comp. Accessed 9-18-2018
Ozempic.com. Accessed 10-2-2018

New product: insulin lispro (Admelog©)

- Rapid-acting insulin
- Availability:
  - Vial: 10 mL (100 units/mL)
  - Pen: 3 mL (100 units/mL)
- Administration: 15 minutes before or immediately after a meal
- Conversion between insulin lispro products (Humalog© and Admelog©) is 1:1 dosing



Lexi-comp. Accessed 9-18-2018
Admelog.com. Accessed 10-2-2018

New product: ertugliflozin (Steglatro©)

- SGLT2 inhibitor
- Administration: oral
  - Dosing: 5 mg once daily, may increase to max of 15 mg per day, if needed
  - Renal impairment:
    - eGFR <60 mL/min/1.73 m^2: do not initiate
    - eGFR <30 mL/min/1.73 m^2: contraindicated
  - Hepatic impairment: not recommended in severe impairment
- Adverse effects:
  - Genital candidiasis: females 9-12% and males 4%
  - Headache: 3-4%
  - Urinary frequency: 2-3%
  - Vulvovaginal pruritus: 2-3%

Lexi-comp. Accessed 9-18-2018

New product: ertugliflozin combination products

- ertugliflozin and metformin (Segluromet©)
  - Dosing: 2 divided doses (max ertugliflozin 15 mg/metformin 2,000 mg/day)

If already on metformin	ertugliflozin 5 mg/day and similar dose of metformin
If already on ertugliflozin	metformin 1000 mg/day and similar dose of ertugliflozin
If already using both	same total daily dose of ertugliflozin and similar dose of metformin

  - Availability:
    - ertugliflozin 2.5 mg with metformin 500 mg or metformin 1000 mg
    - ertugliflozin 7.5 mg with metformin 500 mg or metformin 1000 mg

Lexi-comp. Accessed 9-18-2018

New product: ertugliflozin combination products

- ertugliflozin and sitagliptin (Steglujan©)
  - Dosing: ertugliflozin 5 mg/sitagliptin 100 mg once daily, may increase to ertugliflozin 15 mg/sitagliptin 100 mg once daily, if needed

If already on ertugliflozin	Maintain current ertugliflozin dose with sitagliptin 100 mg/day

  - Availability:
    - ertugliflozin 5 mg/sitagliptin 100 mg
    - ertugliflozin 15 mg/sitagliptin 100 mg

Lexi-comp. Accessed 9-18-2018

New product: exenatide (Bydureon Bcise©)

- GLP-1 receptor agonist
- Administration: subcutaneous injection
  - Dosing: 2 mg once weekly
  - Renal impairment
    - CrCl 30-50 mL/min: use caution
    - CrCl <30 mL/min: use is not recommended
- New device allowing for easier administration

Lexi-comp. Accessed 9-18-2018
Bydureon.com/bydureon-bcise. Accessed 10-2-2018

New product: insulin aspart (Fiasp©)

- Rapid-acting insulin
- Availability:
  - Vial: 10 mL (100 units/mL)
  - Pen: 3 mL (100 units/mL)

- Administration: at the start of a meal or within 20 minutes after starting meal
- Conversion between insulin aspart products (Novolog© and Fiasp©) is 1:1 dosing.

Lexi-comp. Accessed 9-18-2018
Fiasppro.com. Accessed 10-2-2018

Recent FDA Safety Communications:

SGLT2 Inhibitors

Necrotizing fasciitis of the perineum

- Rare, but life-threatening infection
- Overall incidence: 1.6 per 100,000 males annually in the US
- Incidence in patients taking antidiabetic medications:
  - SGLT2 inhibitors over 5 years: 12 cases
    - Average time to onset: 9.2 months
    - All hospitalized and required surgery
    - Associated with each SGLT2 inhibitor except ertugliflozin
  - Other antidiabetic classes over 34 years: 6 cases
    - Insulins, biguanides, sulfonylureas, and DPP-4 inhibitors

FDA Drug Safety Communication: 8-29-2018

Necrotizing fasciitis of the perineum: What you need to know and do

- Symptoms:
  - tenderness, redness, or swelling of genitals or perineum
  - Fever about 100.4° F
  - General feeling of being unwell
  - Pain
- Treatment:
  - Discontinue the SGLT2 inhibitor
  - Start broad-spectrum antibiotics
  - Surgical debridement
- Report to FDA MedWatch

FDA Drug Safety Communication: 8-29-2018

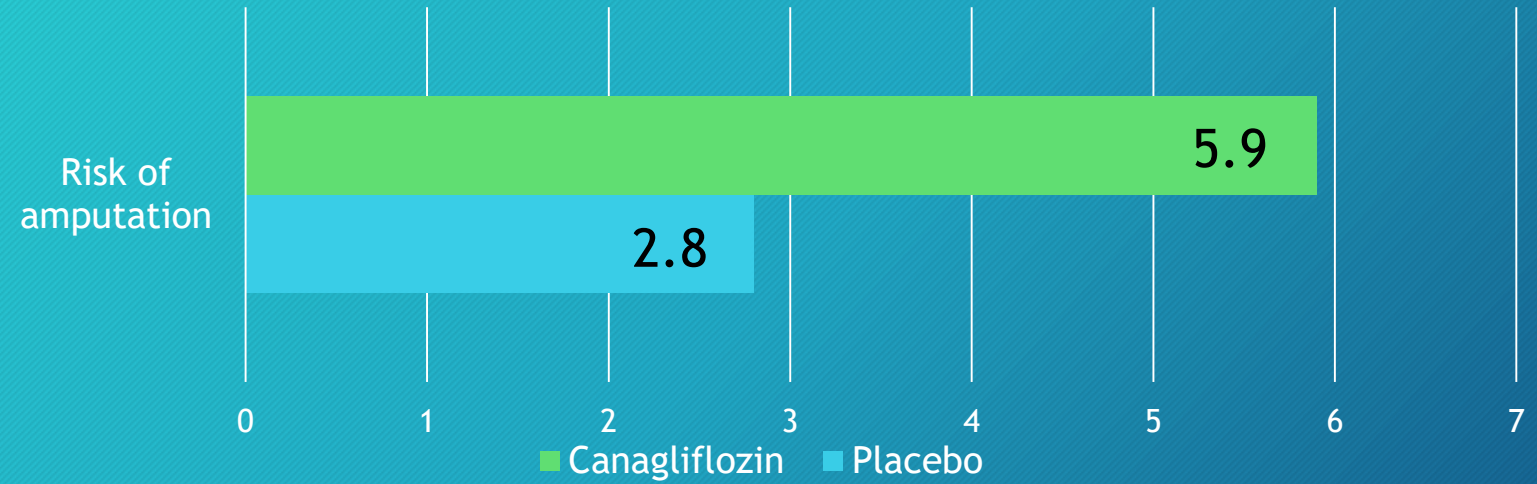
Increased Risk of Leg and Foot Amputations with Canagliflozin (Invokana, Invokamet, Invokamet XR)

- ~2 fold increased risk of amputations with canagliflozin vs. placebo
- Toe and middle of the foot amputations most common
  - Some had more than one amputation, in both limbs
- Consistent with 100 mg and 300 mg dose
- US Boxed Warning

FDA Drug Safety Communication: 5-26-2017

Increased Risk of Leg and Foot Amputations with Canagliflozin (Invokana, Invokamet, Invokamet XR)

- CANVAS
  - Over a year's time, risk of amputation per 1,000 patients treated:

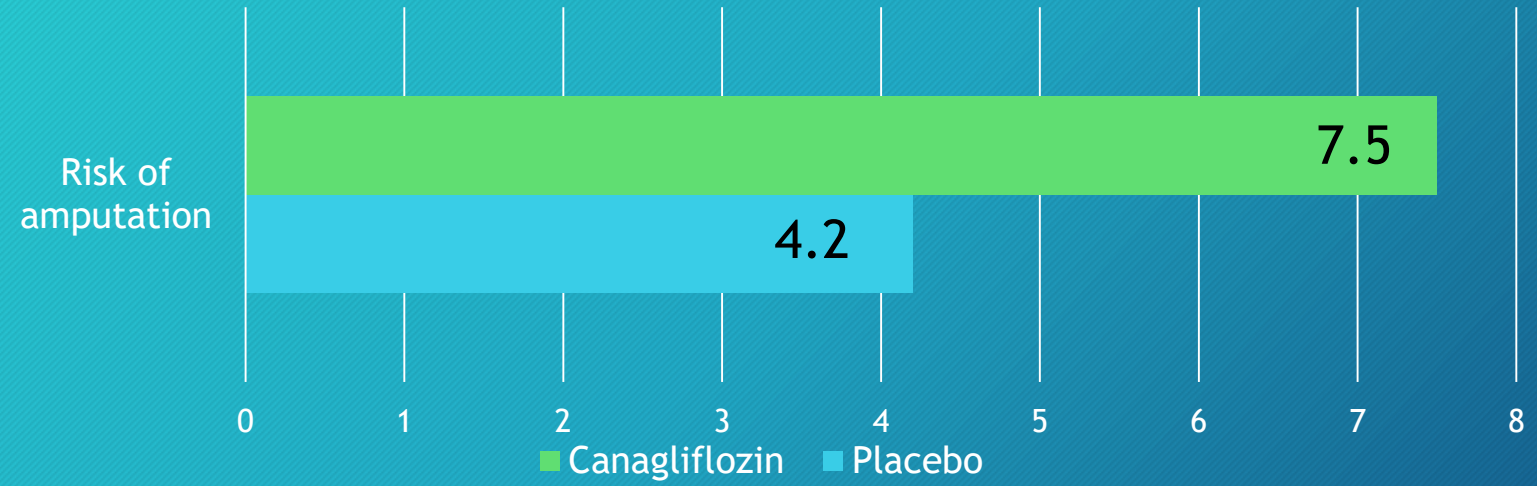


  - Number Need to Harm: 323

FDA Drug Safety Communication: 5-26-2017

Increased Risk of Leg and Foot Amputations with Canagliflozin (Invokana, Invokamet, Invokamet XR)

- CANVAS-R
  - Over a year's time, risk of amputation per 1,000 patients treated:



  - Number Need to Harm: 270

FDA Drug Safety Communication: 5-26-2017

Increased Risk of Leg and Foot Amputations with Canagliflozin: What you need to know and do

- Consider risk factors prior to prescribing canagliflozin:
  - Prior amputation
  - Peripheral vascular disease
  - Neuropathy
  - Diabetic foot ulcers
- Educate patient and monitor for symptoms:
  - New pain or tenderness
  - Sores or ulcers
  - Infections in your legs or feet
- Treatment:
  - Discontinue canagliflozin
- Report to FDA MedWatch

FDA Drug Safety Communication: 5-26-2017

Historical FDA Drug Safety Communications:
Enhanced kidney warnings for canagliflozin and dapagliflozin

- June 2016
- What you need to know and do:
  - Consider predisposing factors:
    - Decreased blood volume
    - Chronic kidney insufficiency
    - Congestive heart failure
    - Other medications: diuretics, ACEIs, ARBs, NSAIDs
  - Baseline and periodic renal function
  - Discontinue SGLT2 inhibitor if acute kidney injury occurs

FDA Drug Safety Communication: 6-2016

Historical FDA Drug Safety Communications: Too much acid in the blood and serious UTIs

- December 2015
- What you need to know and do:
  - Symptoms:
    - Ketoacidosis: nausea, vomiting, abdominal pain, tiredness, trouble breathing
    - UTI: feeling of burning when urinating, urinary frequency or urgency, pain in lower stomach or pelvis, fever, blood in the urine
  - Discontinue SGLT2 inhibitor and start treatment

Historical FDA Drug Safety Communications: Bone fracture risk and decreased bone mineral density with canagliflozin

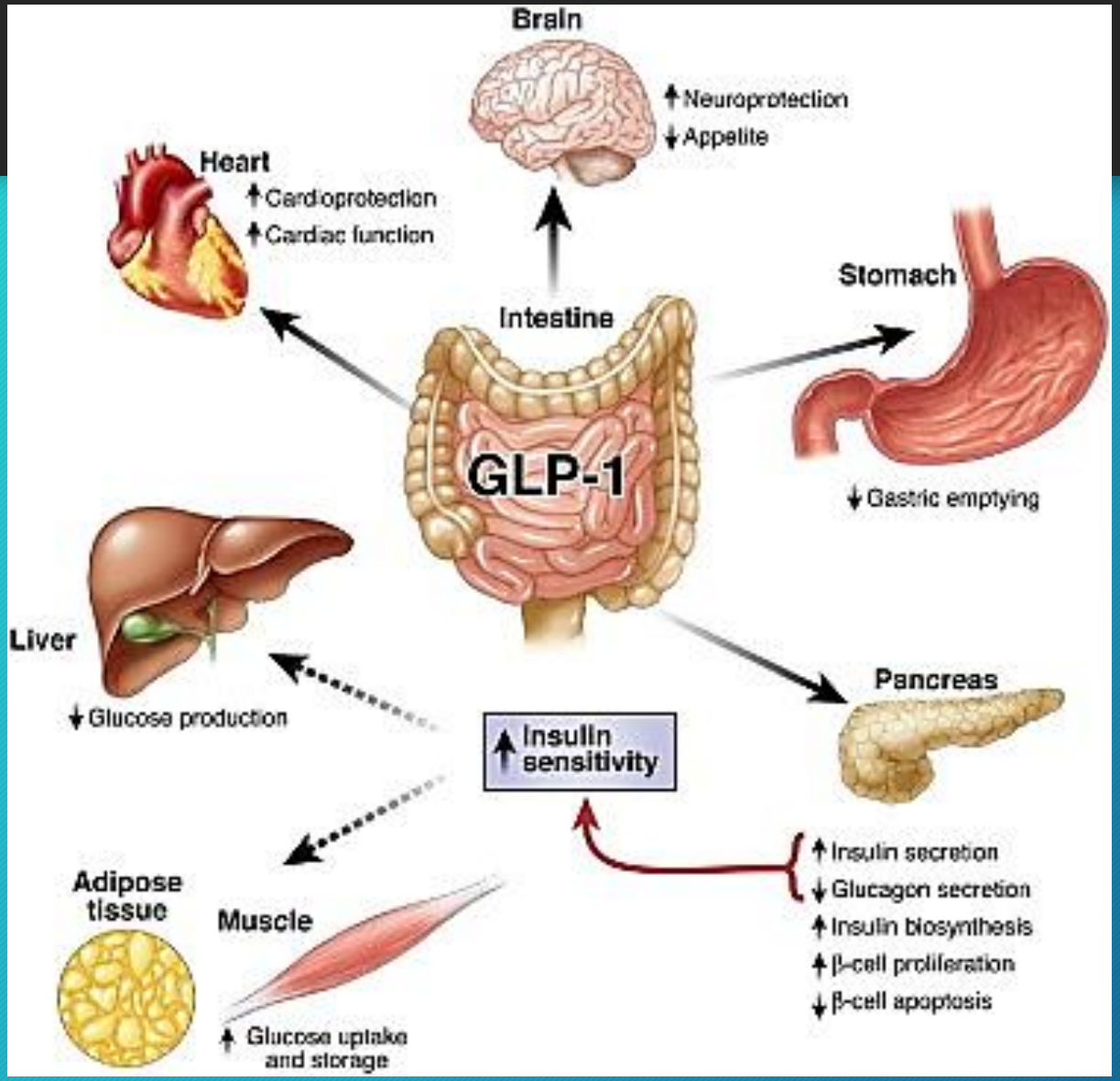
- September 2015
- What you need to know and do:
  - Increased risk of fractures, as early as 12 weeks after initiation
  - Greater loss of BMD at the hip and lower spine with canagliflozin
  - Consider risk factors for fracture prior to prescribing
  - Educate patient about risk factors for fracture
  - Discontinue SGLT2 inhibitor

FDA Drug Safety Communication: 9-2015

Non-Insulin Injectables

GLP-1 agonists

Mechanism of Action



www.gastrojournal.org. Accessed 10-2-2018

GLP-1 agonists: Precautions

- Should not be used if:
  - history of pancreatitis
  - Type 1 diabetes
  - Person or family history of medullary thyroid cancer or multiple endocrine neoplasia 2A or 2B (liraglutide, dulaglutide, exenatide weekly, and semaglutide)
- Injection site reactions are more common compared to insulin
- Antibodies to may develop

UpToDate. Accessed 9-18-2018

Patient Case – 5/5/2017

- RO is a 71 yo male consulted to clinical pharmacy for management of diabetes
- Dietary habits:
  - Cutting back on sweets
  - Eats mainly at home and watches portion sizes
  - Enjoys diet soda and water for beverages
- Exercise habits: walks 2-4 miles daily at the wellness center
- No history of renal or hepatic impairment
- Hypoglycemia: he reports a single reading of 71 about a month ago and treated with glucose tablets

Patient Case – 5/5/2017

- Current diabetes medications:
  - glipizide 15 mg twice daily
  - metformin SA 1000 mg twice daily

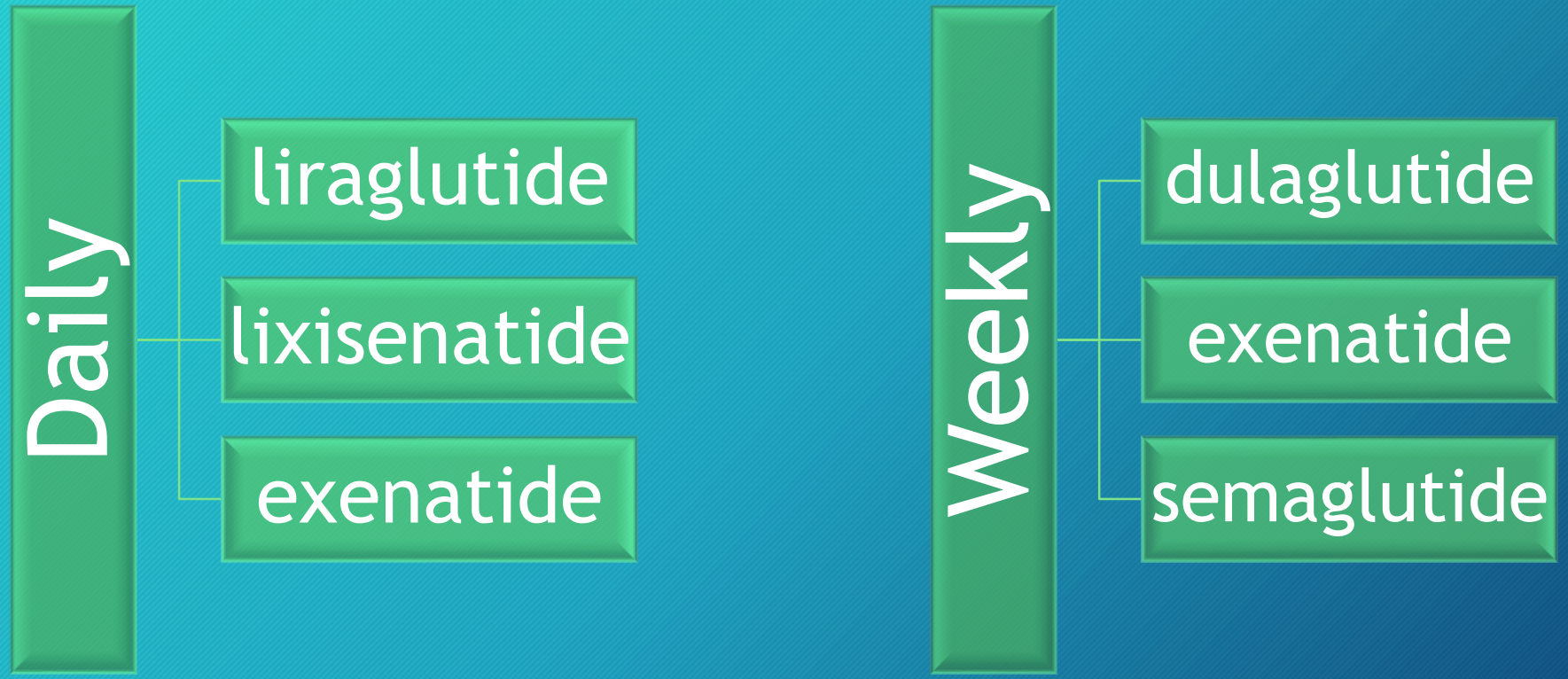
Date	Hgb A1c (%)
5/5/2017	7.5
2/28/2017	8.0
11/29/2016	7.8

- Patient elects to try a GLP-1 agonist

GLP-1 Agonists: Currently Available

- Dulaglutide
- Exenatide
- Liraglutide
- Lixisenatide
- Semaglutide

GLP-1 agonists: Administration



Lexi-comp. Accessed 10-2-2018

Patient Case – 5/5/2017

- Current diabetes medications:
  - glipizide 15 mg twice daily
  - metformin SA 1000 mg twice daily

Date	Hgb A1c (%)
5/5/2017	7.5
2/28/2017	8.0
11/29/2016	7.8

- Patient elects to try a GLP-1 agonist – albiglutide 30 mg once weekly

Patient Case

5/25/17: some hypoglycemia (60s) throughout the day

- Glipizide decreased to 10 mg twice daily

6/8/17: hypoglycemia largely resolved

- No change

6/26/17: Overall average glucose 170; new, itchy rash

- Discontinue albiglutide
- Initiate liraglutide

Patient Case

7/19/17: rash resolved; variable glucose readings

- No change
- Patient to track diet/activity

8/4/17:

A1c 6.6%

- No change: liraglutide 1.2 mg daily, glipizide 10 mg twice daily, metformin SA 1500 mg daily

12/12/17:

A1c 6.6% with PCP

- No change

Patient Case

4/18/18:

A1c 7.0%

- Increase liraglutide to 1.8 mg daily

5/16/18:

Average fasting glucose 143

- Pt agreeable to adjusting bedtime snack (often eating chips)

7/16/18:

A1c 6.7%

Nausea and vomiting and constipation

- Discontinue liraglutide
- Initiate dulaglutide 0.75 mg once weekly

GLP-1 agonists: Common Adverse Events

	Nausea (%)	Diarrhea (%)	Vomiting (%)	Abdominal Pain (%)	Injection Site Reaction (%)
Dulaglutide	12-21	9-13	6-13	7-9	<1
Exenatide IR	8	1-2	4	--	--
Exenatide ER	8-11	4-11	3	<1	17
Liraglutide	18-20	10-12	6-9	--	2
Lixisenatide	25	8	10	2	4
Semaglutide	--	9	5-9	6-7	<1

Lexi-comp. Accessed 10-2-2018

Patient Case

8/24/18:

GI symptoms resolved and no bruising at injection sites

- No change
- Continue dulaglutide 0.75 mg once weekly, glipizide 10 mg twice daily, metformin SA 1500 mg daily

9/17/18:

Transient increase in glucose from oral prednisone, otherwise average fasting glucose 124

- No change
- Recheck A1c 10/2018

U-500 and Concentrated Insulins

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Patient Case

- RW is a 62 yo male with Type 2 Diabetes Mellitus. He was initially seen in clinic on 4/5/17.
  - A1c 9.7% (11.1% 3 months prior)
  - Weight: 375 lbs, BMI 52
  - Insulin glargine 50 units QAM and 60 units QPM
  - Insulin aspart 40 units TID before meals
  - EGFR 36 (unable to use metformin due to variable kidney function)
  - ADR to pioglitazone

Patient Case

Diet poorly controlled and refuses dietitian consult

Reports compliance isn’t great and he will frequently forget his insulin

Asked to improve diet and to work on remembering to take his insulin when indicated prior to next visit

Patient Case – 4/20/17

- Improved compliance
- Trying to work on reducing portion sizes
- Increased insulin glargine to 60 units BID and discussed U-500 which he was willing to try

SMBG			
DATE	AM	LUNCH	PM
5-Apr	216	156	363
6-Apr	226		413
7-Apr	217	194	
9-Apr	200	161	241
10-Apr	169	167	93
11-Apr	136	152	242
12-Apr	150	170	236
13-Apr	147	206	
14-Apr	138	134	
15-Apr		140	139
16-Apr	214	170	
17-Apr	184	117	
18-Apr	164	286	264
19-Apr	185	198	
20-Apr	198		
AVERAGE	182	173	249
OVERALL AVERAGE			201

Patient Case – 5/8/17

- Blood sugars remain elevated
- Insulin glargine 60 units BID + insulin aspart 40 units TID with meals (TDD 240 units)
- Agreeable to switching to U-500

- Discontinued insulin glargine and insulin aspart
- Initiated U-500 Kwik Pen
  - 95 units with breakfast
  - 70 units with lunch
  - 70 units with dinner

SMBG			
AM	Lunch	Supper	
198		217	
140	129		
226	145	107	
163	216	142	
182	146	151	
143	163	96	
172	171	73	
108	212	174	
179	173		
159		170	
193	133	165	
187	248	172	
162	200		
203	196	141	
144	140	88	
168	163		
220	129	126	
153	102	103	
161	120		
172	164	138	AVERAGE

Insulin U-500

HumuLIN R U-500 Kwik Pen

- Insulin 500 units/mL
- Indicated in patients using >200 units of insulin daily
- Dials 5 units of insulin with each click
- Able to administer 5-300 units in one injection

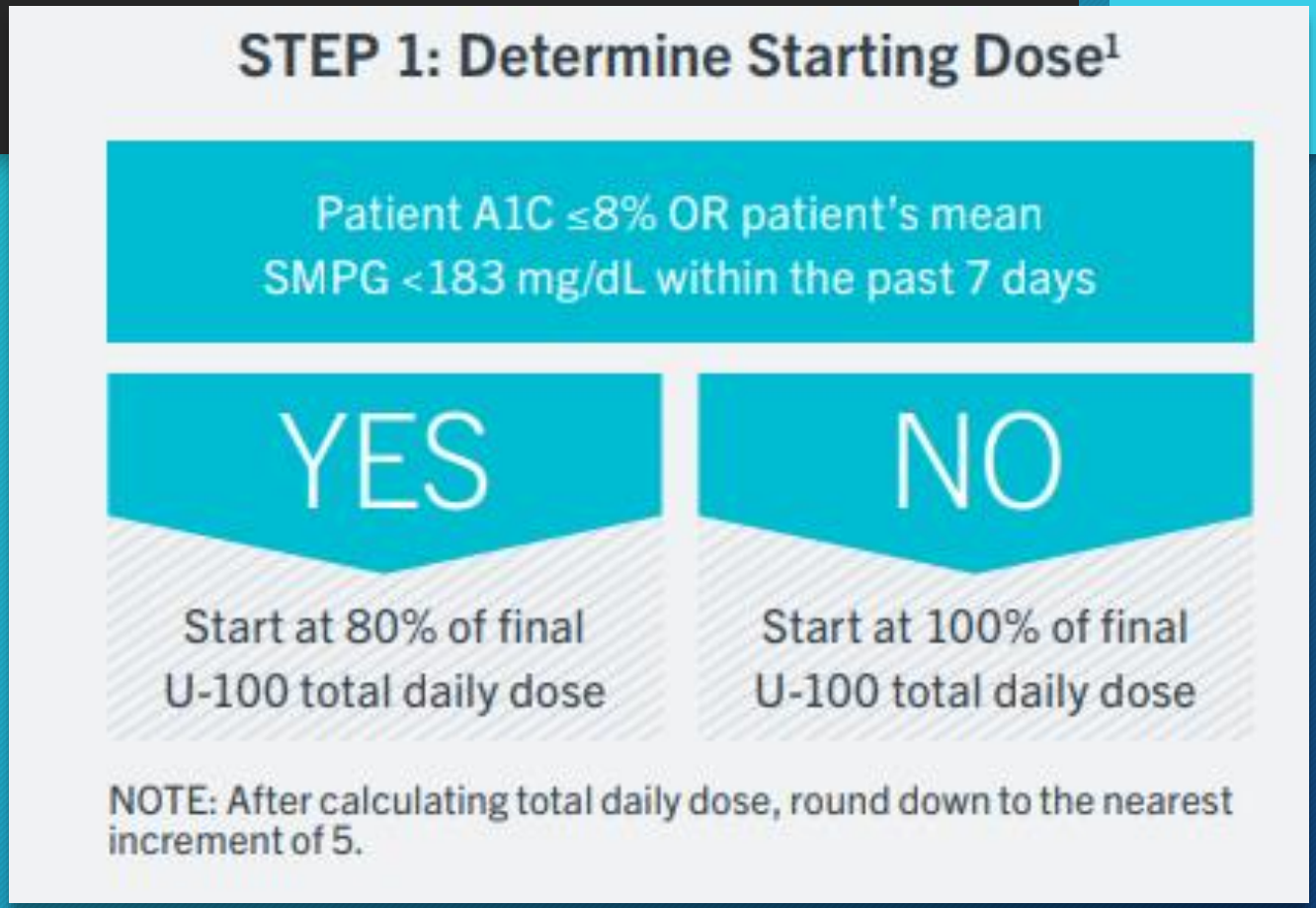
Humulin R U-500, Eli Lilly. 1997
Lexi-Comp. Accessed 9-4-18.

Kinetics/Pharmacodynamics

- Onset of action: <15 minutes
- Average peak: 50 unit dose – 4 hours
  100 unit dose – 8 hours
- Duration: 13-24 hours (average 21 hours)
- Average half-life: 4.5 hours
- Hypoglycemia can develop as long as 18-24 hours after injection

Humulin R U-500, Eli Lilly. 1997
Lexi-Comp. Accessed 9-4-18.

Transitioning from U-100 to U-500



Humulin R U-500, Eli Lilly. 1997
Lexi-Comp. Accessed 9-4-18.

STEP 2: Determine Dose Proportions[1]

TID Dose Proportions

BEFORE BREAKFAST	40%
BEFORE LUNCH	30%
BEFORE DINNER	30%

BID Dose Proportions

BEFORE BREAKFAST	60%
BEFORE DINNER	40%

Administer 30 minutes before meals.
Decrease dose by half if meal is skipped.

Humulin R U-500, Eli Lilly. 1997
Lexi-Comp. Accessed 9-4-18.

Dose Adjustments

INSULIN DOSE TO ADJUST	PLASMA-EQUIVALENT GLUCOSE VALUE*	SMPG (mg/dL)	DOSE TITRATION†
PRE-BREAKFAST	MEDIAN§ PRE-LUNCH SMPG	≤70‡	-10%
		71-130	No change in dose
PRE-LUNCH	MEDIAN§ PRE-DINNER SMPG	131-180	+5%
		181-220	+10%
PRE-DINNER	MEDIAN§ PRE-BREAKFAST SMPG	>220	+15%

Humulin R U-500, Eli Lilly. 1997
Lexi-Comp. Accessed 9-4-18.

Dose Adjustments

INSULIN DOSE TO ADJUST	PLASMA-EQUIVALENT GLUCOSE VALUE*	SMPG (mg/dL)	DOSE TITRATION†
PRE-BREAKFAST	MEDIAN§ PRE-DINNER SMPG	≤70‡	-10%
		71-130	No change in dose
PRE-DINNER	MEDIAN§ PRE-BREAKFAST SMPG	131-180	+5%
		181-220	+10%
		>220	+15%

Humulin R U-500, Eli Lilly. 1997
Lexi-Comp. Accessed 9-4-18.

Dose Adjustments

- Prioritize dose adjustments for hypoglycemia versus dose
- May titrate both BID doses at same visit
- Titrate no more than 2 of 3 TID doses at the same visit
- Check blood glucose before each meal and at bedtime
- May require overnight checks if dose was increased within the past 48 hours

Humulin R U-500, Eli Lilly. 1997
Lexi-Comp. Accessed 9-4-18.

Patient Case

- Veteran continued on U-500 for ~10 months
- 3/2018
  - Insulin U-500 100/55/50 units before breakfast/lunch/supper
  - A1c 7.6% and dose adjustments difficult due to hypoglycemia
  - BG ranged from 71-358mg/dL

Patient Case

- Agreeable to switch to insulin degludec (U-200) + insulin aspart
- Total daily insulin dose (U-500) = 205 units
- Split 50:50 between basal & bolus insulin

- DISCONTINUE U-500 insulin
- INITIATE insulin degludec (200 U/mL) 100 units daily
- INITIATE insulin aspart 30 units before meals

Insulin U-200

Insulin degludec (Tresiba)

- Insulin degludec 200 units/mL
- Steady release throughout the day
- Blood sugar control beyond 24 hours
- Delivers in 2 unit increments
- Can administer up to 160 units in a single injection

Tresiba, Novo Nordisk. 2015.
Lexi-Comp. Accessed 9-21-18

Kinetics/Pharmacodynamics

- Onset of action: ~1 hour
- Average peak: 9 hours (after 8 daily doses)
- Duration: at least 42 hours
- Average Half-life: 25 hours

Tresiba, Novo Nordisk. 2015.
Lexi-Comp. Accessed 9-21-18

Dosing

- Initial dosage (insulin-naive): 10 units subQ once daily
- Initial dosage (insulin-experienced): Initiate with same unit dose as the total daily long or intermediate-acting insulin unit dose
- Maintenance dose: Give subQ once daily at any time of the day.
  - Titrate to clinical effect with dose increases every 3 to 4 days as needed

Tresiba, Novo Nordisk. 2015.
Lexi-Comp. Accessed 9-21-18

Insulin U-300

Insulin glargine (Toujeo)

- Insulin glargine 300 units/mL
- Provides steady release throughout the day
- Blood glucose control beyond 24 hours
- After first use, can be stored outside of the refrigerator for up to 6 weeks

Toujeo, Sanofi-Aventis. 2018.
Lexi-Comp. Accessed 9-26-18.

Insulin glargine (Toujeo)

Toujeo, Sanofi-Aventis. 2018.

Kinetics/Pharmacodynamics

- Onset of Action: 6 hours
- Average peak: 12-16 hours (dose dependent)
  - Maximum glucose lowering effect may take up to 5 days with repeat dosing; at steady state
- Duration: >24 hours

Toujeo, Sanofi-Aventis. 2018.
Lexi-Comp. Accessed 9-26-18.

Dosing

- Initial: 0.2 units/kg once daily
  - Product labeling does not specify an initial max dose
- Titration: Adjust based on patient response
  - To minimize hypoglycemia risk, avoid titrating the dose of Toujeo more often than every 3-4 days
- Higher daily dose of Toujeo generally required to achieve the same level of glycemic control as with Lantus

Toujeo, Sanofi-Aventis. 2018.
Lexi-Comp. Accessed 9-26-18.

Patient Case

- 7/10/18 – A1c 7.8%
- Veteran reported a lot of life stressors (high grade prostate cancer requiring prostatectomy, son getting divorced)
- Admits to poor diet choices and would like to work on this

Patient Case

- 9/19/18
- Continues to try to work on his diet and is following with mental health due to his depression
- Average BG is 179mg/dL

- INCREASE insulin degludec (200 U/mL) to 120 units daily
- INCREASE insulin aspart to 40 units before meals + correction factor

10-Sep	226	166	179	186
11-Sep	180	138	141	192
12-Sep	183	253	215	
13-Sep	178	120	110	188
14-Sep	179	122		231
15-Sep	225	167	243	
16-Sep	221	179	232	
17-Sep	201	162	181	190
18-Sep	178	233	102	162
AVERAGE	179	153	200	190
OVERALL	AVERAGE		179	

References

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