SMF PCP Treatment & Referral Guideline
for Type 2 Diabetes Mellitus
Developed July 26, 2006
Revised September, 2011

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I. **Type 2 Diabetes**
   A “one time” consultation to the endocrinologist with return to PCP for ongoing care is applicable, if all of the following have been met before a consult request is made.

   The PCP actively works with the patient and consistently sets the expectation that the PCP and the pt will work together to improve and control diabetes. This implies that patients are routinely scheduled with the PCP offices; at least quarterly, to monitor progress, review home testing results and go over lab results. PCPs let the pts know an Endocrine consult is a one time opinion to help the PCP manage the diabetes and pts are encouraged to make a follow up appt with the PCP shortly after the consultation to go over the recommendations.

   Patients have been actively managed in the PCP practice with at least three (3) visits 6-12 weeks apart where lifestyle modification, blood sugar results and medication changes have been applied. These recommendations and med changes need to be clearly documented in the medical record

   A) Patients have tried all categories of drugs in combination unless medically contraindicated. This includes:
      a) Insulin secretagogues 
      b) Biguanides 
      c) Thiazolidinediones 
      d) Incretins 
      e) Insulin
   B) Patients have been seen by the Diabetes Education Team within the previous 12 mos and worked with the education team on the treatment protocols in place. These include the oral medicine titrations and the insulin guidelines.
   C) Patients are actively involved in their care and willing to check their blood sugar a minimum of twice a day, while working on portion control and exercise.

**APPROVAL:**

[Signature]
SMF Medical Director

December 14, 2011
Date

**Approval / Revision Summary:**
SMF QM/UM Committee          Date: 12/14/2011
SPA Steering Committee         Date: FYI
**GENERAL RECOMMENDATIONS**

- Start insulin if A1C and glucose levels are above goal despite optimal use of other diabetes medications. (Consider insulin as initial therapy if A1C very high, such as > 10.0%) 6,7,8
- Start with **BASAL INSULIN** for most patients 6,7,8
- Consider the following goals 1,6
  
  **ADA A1C Goals:**
  - A1C < 7.0 for most patients
  - A1C > 7.0 (consider 7.0-7.9) for higher risk patients
    1. History of severe hypoglycemia
    2. Multiple co-morbid conditions
    3. Long standing diabetes
    4. Limited life expectancy
    5. Advanced complications or

  **ADA Glucose Goals:**
  - Fasting and premeal glucose < 130
  - Peak post-meal glucose (1-2 hours after meal) < 180
  - Difference between premeal and post-meal glucose < 50
  
  *for higher risk patients individualize glucose goals in order to avoid hypoglycemia*

**BASAL INSULIN**

- **Long-acting:**
  - Glargine (Lantus®)
  - Detemir (Levemir®)

- **Intermediate-acting:**
  - NPH

  *Note: NPH insulin has elevated risk of hypoglycemia so use with extra caution* 6,8,15,17,32

- Basal insulin is best starting insulin choice for most patients (if fasting glucose above goal). 6,7,8
- Start one of the intermediate-acting or long-acting insulins listed above. 6,7 Start insulin at night. 6,8,20,29
- When starting basal insulin: Continue secretagogues. Continue metformin. 7,8,20,29
- *Note: if NPH causes nocturnal hypoglycemia, consider switching NPH to long-acting insulin.* 17,25,32

**STARTING DOSE:**

- **Start dose:** 10 units 6,7,8,11,12,13,14,16,19,20,21,22,25

  Consider using a lower starting dose (such as 0.1 units/kg/day) 32 especially if patient is thin or has a fasting glucose only minimally above goal. 17,18

**TITRATION**

Teach patient to self titrate 1 unit every 1 day until average fasting glucose < 130* 16

(*Inform patient to hold titration until further evaluation if develops any hypoglycemia)

or

Tritrate 1 time per week as per table below until average fasting glucose < 130 10,11,13,14,15,17,18,20,21,26,28

- Fasting glucose > 180 increase 8u
- Fasting glucose 160-180 increase 6u
- Fasting glucose 140-160 increase 4u
- Fasting glucose 130-140 increase 2u
- Fasting glucose 70-130 no change
- Fasting glucose < 70 decrease 2u or 10%

Within one to two months, evaluate post-meal glucose pattern 6,7,8

If post-meal glucose levels > 50 mg/dl above premeal: consider **ADD PRANDIAL INSULIN** 6,7,8

Note: If patient unable to do multiple daily injections, consider switching to **MIXED INSULIN** instead of adding prandial insulin (see pg. 3 for switching to mixed insulin). (Mixed insulin is more likely to cause hypoglycemia 6,18 and generally requires a fixed meal schedule)*
PRANDIAL INSULIN

Rapid Acting: Lispro (Humalog®)
Aspart (Novolog®)
Glulisine (Apidra®)

Short Acting: Regular Note: Regular insulin has longer peak and extra risk of hypoglycemia so use with caution

- Add prandial insulin to basal insulin if post-meal blood glucose levels are above goal.
- Start one of the prandial insulins listed above.
- When adding prandial insulin: Stop secretagogues. Continue metformin. Continue basal insulin (may need to re-adjust dose).
- Give rapid acting insulins less than 15 minutes before meal. Give Regular insulin 30 minute before meals.
- Note: after maximizing prandial and night-time basal insulin dose, may need to consider adding a morning dose of basal insulin if pre-dinner glucose remains above goal (more likely to be necessary if using NPH).

STARTING DOSE: 4 units qAC

Alternative dose: 7-10% of basal insulin dose qAC

- Instruct patients to eat carb consistent meals when first starting prandial insulin.
- May consider start prandial insulin with largest meal only (if so, may consider postpone stopping secretagogue until using prandial insulin for 2 or more meals per day)
Note: if on NPH bid, may hold lunch time prandial dose

Consider adding pre-meal Correction Factor (CF): Add 1 unit for each 50 that pre-meal glucose is > 130

Mixed insulin:

MIXED INSULIN

75/25 Lispro Mix (Humalog® Mix) or 50/50 Lispro Mix (Humalog® Mix)
70/30 Aspart Mix (Novolog® Mix)
70/30 NPH/Regular Note: 70/30 NPH/Regular insulin has elevated risk of hypoglycemia so use with extra caution

- Mixed insulin is an option for patients who are unable to do multiple injections and who have fixed meal schedules.
- Mixed insulin is more likely to cause hypoglycemia compared to basal and prandial insulins.
- Start one of the mixed insulins listed above.
- When starting mixed insulin: Stop secretagogues. Continue metformin. (If already on other insulin, then see guideline for switching to mixed insulin on page 3).

TITRATE: Titrate 1-2 units every 2-3 days until post-meal glucose < 180

(May consider different doses for different meals)

TITRATE:

Titrated 1-2 units every 2-3 days until post-meal glucose < 180

(May consider different doses for different meals)

TITRATE:

Titrated 1-2 units every 2-3 days until average target glucose < 130

OR

Titrated 1-2 times per week such as per table below until average target glucose < 130

- Target glucose > 200 ↑ by 4 units
- Target glucose 131-200 ↑ by 2 units
- Target glucose 70-130 No change
- Target glucose < 70 ↓ 2-4 units or by 10%

- May require different doses for pre-breakfast and pre-dinner
- May consider adding pre-lunch dose as well if needed

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**Switching Mixed Insulin to Basal/Prandial Insulin**

**Selection of Patients:**
- Patient has persistent hypoglycemia episodes or
- Patient has excess glucose variability or
- Patient wants a more flexible meal schedule

- Determine total daily mixed insulin dose (TDD)
- Stop mixed insulin
- Start basal insulin qHS and prandial insulin qAC.

**Starting dose of basal insulin:**
50% TDD (total daily mixed insulin dose) qHS

**Starting dose of prandial insulin:**
10% TDD (total daily mixed insulin dose) qAC

**Starting dose of breakfast dose:**
30-40% of total daily insulin dose

**Target glucose for titration is pre-dinner glucose.**

**Switching from Basal or Basal/Prandial Insulin to Mixed Insulin**

**Selection of Patients:**
- Difficulty taking multiple injections daily
- Stable consistent meal schedule
- Stable glucose pattern and no hypoglycemia episodes

- Determine total daily insulin dose (TDD)
- Stop both Basal and Prandial insulin
- Start Mixed insulin before breakfast and before dinner.

**Starting dose of dinner dose:**
30-40% of total daily insulin dose

**Target glucose for titration is fasting glucose.**

**Switching Insulin Types**

**Switching from NPH to Lantus/Levemir:** consider if patient has nocturnal hypoglycemia or persistent day time hyperglycemia:

Start Lantus/Levemir before bed at 50%-70% of total daily NPH dose* (then titrate per basal insulin guideline)

**Switching from Lantus/Levemir to NPH:** consider if patient needs to switch due to cost:

Start NPH before bed at 40% of total daily Lantus/Levemir dose* (then titrate per basal insulin guideline)

Caution:
- Watch for nocturnal hypoglycemia
- Evaluate day time glucose levels. If necessary consider add morning NPH dose as well
- If adding morning NPH dose, consider lower lunch prandial insulin due to midday NPH peak

**Switching from Regular to Humalog/Novolog/Apidra:** consider if patient has day time hypoglycemia:

Start Humalog/Novolog/Apidra at 80% of current Regular Insulin mealtime dose* (then titrate per prandial insulin guideline)

**Switching from Humalog/Novolog/Apidra to Regular Insulin:** consider if patient needs to switch due to cost:

Start Regular Insulin at 80% of current mealtime Humalog/Novolog/Apidra dose* (then titrate per prandial insulin guideline)

Caution:
- Watch for day time hypoglycemia
- Need to take Regular Insulin injection 30 minutes before meals

**Pre-Operative Diabetes Guidelines**

**General Recommendations**

**Day before surgery:** Take all regular diabetes pills and oral medications (except **hold** evening metformin dose). Take Byetta, Victoza and Symlin as usual.

**Day of surgery**: **Hold** all regular diabetes pills and oral medications. **Hold** Byetta, Victoza and Symlin.

*Tell patient to treat any hypoglycemia with 15 gms of glucose gel or glucose tabs or 4 ozs of clear juice such as apple or cranberry.

**Adjusting Insulin**

**Day before surgery:**
- Basal Insulin: Take 80% of usual nighttime dose*
- Prandial Insulin: Take as usual
- Mixed Insulin: Take 80% of usual nighttime dose*

**Morning of surgery:**
- Basal Insulin: If patient regularly takes basal insulin in the morning, take 80% of usual morning dose*
- Prandial Insulin: **Hold**
- Mixed Insulin: **Hold**

*NOTE: consider alternate dose adjustment if low or high glucose levels on current insulin dose!
### ADDITIONAL INFORMATION:

**Alternate self titration for basal insulin**

May consider self titrating basal insulin by increasing dose 2 unit every 2-3 days until average fasting glucose is < 130. Self titration of 2 unit intervals may be easier for patients using insulin syringes.

**Other diabetes medication in combination with insulin**

- **Metformin**: Continue if able because helps prevent weight gain when patient on insulin
- **Secretagogues**: (sulfonylureas and meglitinides): Consider continuing when patient is on basal insulin only. Stop when patient is on prandial or mixed insulin.

**Other Diabetes Medications**: decision to continue or discontinue other diabetes medications should be made with consideration of multiple individual patient characteristics.

**Note**: once patient’s glucose levels are controlled with insulin, it may occasionally be possible to stop insulin and continue or switch to oral medications depending of the stage of the diabetes and changes in other individual patient characteristics.

**Example of correction factor using 1800 Rule**

- Patient on 60 units basal insulin. Total Daily Dose (TDD) is 60 units. Correction Factor (CF) = 1800 / 60 = 30. If pre-meal glucose = 230, blood glucose is 150 mg/dl above goal of 130; Correction is 150/30 = 5 units. Give 5 units in addition to prandial insulin dose being used to cover meal.

**Example of Insulin with prandial dose of 4 units and correction factor of 1:50, correcting down to 130**

<table>
<thead>
<tr>
<th>Pre-meal Glucose Level</th>
<th>Prandial Insulin Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>70-130</td>
<td>4 units</td>
</tr>
<tr>
<td>130-180</td>
<td>5 units</td>
</tr>
<tr>
<td>180-230</td>
<td>6 units</td>
</tr>
<tr>
<td>230-280</td>
<td>7 units</td>
</tr>
<tr>
<td>280-330</td>
<td>8 units</td>
</tr>
<tr>
<td>330-380</td>
<td>9 units</td>
</tr>
<tr>
<td>380-430</td>
<td>10 units</td>
</tr>
<tr>
<td>&gt;430</td>
<td>11 units</td>
</tr>
</tbody>
</table>

**Example of carbohydrate ratio using 500 Rule**

- Patient on 50 units basal insulin daily. Total Daily Dose (TDD) is 50 units. Insulin to Carbohydrate Ratio (I:C Ratio): 500/50 = 1:10 units. For a 60 gm carbohydrate meal = 60/10 = take 6 units.

**Mealtime Advice**

- Take rapid acting prandial and mixed insulins just before a meal. At restaurants only take once food actually arrives at table.
- Take Regular insulin 30 minutes before meals.

**Hypoglycemia**

- Tell patient to carry rapidly absorbed carbohydrate source at all times and teach friends and family about how to treat low glucose. Treat low glucose (<70) as per Rule of 15’s: Give 15 gm of rapidly absorbed carbohydrate (ie: 1/2 cup juice or 4 glucose tabs). Recheck glucose level in 15 minutes. Give another 15 gm of carbohydrate if glucose still < 70. Repeat until the glucose level higher than 70. Once glucose level returns to normal, consider follow with a snack or meal. Inform provider of hypoglycemia episodes at next appointment. If severe (unconscious, seizures) call 911 and give glucagon (1.0 for adult, 0.5 for child < 50 lbs) if available. Prescribe glucagon kit for high risk patient to have at home.

**Identification**

- Carry personal ID and wear medical ID.

**Insulin Device**

- Consider insulin pen if able for patients with vision, dexterity or cognition difficulties or for patient convenience. Note insulin pens cost more than insulin vials. However, total cost of insulin pen is potentially lower than vial if patient’s daily insulin dose is low (since less unused insulin needs to be discarded at end of month). Insulin pens may not be covered by insurance.

**Storage**

- Refrigerate insulin until opened. Discard after expiration date. Once opened can be kept at room temperature. Avoid heat. Replace insulin vial or pen as required per specific insulin package insert.

**Syringes and Needles**

- For pen consider use pen needles that are 31 or 32 gauge and 5 mm to 8 mm. For vials consider use syringes that are 0.3-1.0 cc with ultrafine 5/16” 31 gauge needles. Instruct patient to leave needle in skin for 5 or more seconds after injection completed.

**Exercise**

- Low glucose levels may occur during or after exercise. Carry glucose source when exercising. Check glucose before and during exercise. If patient has low glucose levels associated with exercise: consider decreasing preceding prandial insulin dose (if within several hours before exercise) and/or taking extra carbohydrates before or during exercise.

**Education**

- All patients should receive Diabetes Self Management Training (DSMT) and Medical Nutrition Therapy (MNT) by certified diabetes educator if possible.
LITERATURE SEARCH AND RATING PROCESS

The identification and rating of the body of evidence to support the Type 2 Diabetes Insulin Guidelines followed a three-step process:

1. Pertinent articles for review were identified by a Medline search including the key words: "Diabetes Mellitus, Type 2 drug therapy, Hypoglycemic Agents, Insulin, Algorithms, Titrate, Titration, Bolus, and Basal." The search was limited to 2005-2010 and the language English. Older clinical trials evaluating Regular insulin were included, since none were available from 2005-2010. The most recent ADA and AACE consensus statements, position statements and technical reviews on diabetes care topics were also identified. Insulin package insert recommendations were obtained from Lexi-Comp, Online.

2. Experts in diabetes care then examined the list of articles and included only those that were identified as randomized controlled clinical trials examining the initiation and titration of insulin, the most recent general consensus statements, technical reviews, or position statements by ADA and AACE, the most recent insulin review article by the American Academy of Family Practice, and the Lexi-Comp online insulin package insert recommendations.

3. The articles were reviewed and the body of evidence was rated using a system adopted from the ADA grading system for clinical practice recommendations. (A) Clear evidence from well-conducted, generalizable, randomized controlled trials that are adequately powered, including:
   - Evidence from a well-conducted multicenter trial
   - Evidence from a meta-analysis that incorporated quality ratings in the analysis
   - Compelling non-experimental evidence, i.e., "all or none" rule developed by Center for Evidence Based Medicine at Oxford
   - Supportive evidence from well-conducted randomized controlled trials that are adequately powered, including:
     - Evidence from a well-conducted trial at one or more institutions
     - Evidence from a meta-analysis that incorporated quality ratings in the analysis
   (B) Supportive evidence from well-conducted cohort studies:
     - Evidence from a well-conducted prospective cohort study or registry
     - Evidence from a well-conducted meta-analysis of cohort studies
   (C) Supportive evidence from poorly controlled or uncontrolled studies
     - Evidence from randomized clinical trials with one or more major or three or more minor methodological flaws that could invalidate the results
     - Evidence from observational studies with high potential for bias (such as case series with comparison to historical controls)
     - Evidence from case series or case reports
   (E) Conflicting evidence with the weight of evidence supporting the recommendation

GENERAL INFORMATION: Consensus Statements and Reviews


BASAL INSULIN (A-level evidence)


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BASAL INSULIN (A-level evidence), continued


27. Robbins DC et al. Mealtime 50/50 basal + prandial insulin analogue mixture with a basal insulin analogue, both plus metformin, in the achievement of target HbA1c and pre- and postprandial blood glucose levels in patients with type 2 diabetes: a multinational, 24-week, randomized, open-label, parallel-group comparison. Clin Ther. 2007 Nov;29(11):2349-64.


PRANDIAL INSULIN (A-level evidence)

33. Anderson J H; Brunelle R L; Koivisto V A; Pfutzner A; Trautmann M E; Vignati L; DiMarchi R Reduction of postprandial hyperglycemia and frequency of hypoglycaemia in IDF patients on insulin-analog treatment. Multicenter Insulin Lispro Study Group. Diabetes Feb 1997 46 (2) p265-70.


MIXED INSULIN (A-level evidence)


Type 2 Diabetes: Byetta® (exenatide) Guideline

Selection of Patients
HbA1c > 7% and
- Not on insulin
- No significant gastroparesis, severe GI disease, severe nausea, or history or risk of pancreatitis.
- Not recommended in ESRD or severe renal impairment (CrCl < 30 mL/min); use cautiously in renal transplantation.

Start Byetta® (exenatide) 5 mcg BID SQ
- Administer within 60 min prior to morning and evening meal (or prior to the 2 main meals of the day, approximately ≥ 6 hours apart).
- Continue all current tolerated oral diabetic medications except DPP4-inhibitors (e.g. Januvia® (sitagliptin)).
- Consider reducing sulfonylurea to 50% current dose to reduce the risk of hypoglycemia unless baseline glucose is significantly elevated at initiation of Byetta®.
- Use 5 or 8 mm ultrafine pen needles with Byetta®.
- Store Byetta® in refrigerator until opened. Once opened, may be stored at room temperature (< 77°F). Discard 30 days after first use.
- Many patients develop nausea. If severe nausea, stop Byetta®. If mild nausea, may continue use as nausea diminishes over time. Avoid if dehydration from nausea and vomiting.
- Possible increased risk of pancreatitis. If severe abdominal pain or severe nausea and vomiting, stop Byetta® (exenatide) and check lipase/amylase.

Evaluate glucose pattern after 1 month

Pattern low
- Cut dose of sulfonylurea (eliminate if needed)

Pattern at goal
- No change

Pattern high
- Evaluate glucose pattern

Increase Byetta® (exenatide) to 10 mcg BID SQ * If well tolerated

Dose Adjustments
CrCl > 50 ml/min: No adjustment necessary.
CrCl 30–50 ml/min: Use caution when initiating or escalating doses.
CrCl < 30 ml/min: Not recommended.

Evaluate glucose pattern

Pattern low
- Cut dose of sulfonylureas (eliminate if needed)

Pattern at goal
- No change

Pattern high
- Consider switch Byetta® (exentaide) to insulin

Diabetes Type 2 Basal Insulin Guideline
FDA has determined that a Risk Evaluation and Mitigation Strategy (REMS) is necessary to ensure that the benefits of VICTOZA (liraglutide) outweigh the potential risk of medullary thyroid carcinoma and the risk of acute pancreatitis.

**Selection of Patients:**
- HbA1c > 7% and
- Not on insulin or Byetta (exenatide)
- Taking at least 1 oral diabetic medication (e.g. metformin) – not recommended 1st line
- No history or risk of pancreatitis
- No personal or family history of medullary thyroid carcinoma or MEN2*

**Start Victoza® (liraglutide) 0.6 mg SQ once daily for 1 week (starting dose – not effective for glycemic control)**
- Administer once daily at any time of the day, independently of meals.
- SQ injection into abdomen, thigh or upper arm – injection site and timing may be changed independent of dose adjustment.
- Continue all current tolerated oral diabetic medications except DPP4-inhibitors (e.g. Januvia® (sitagliptin)).
- Reduce sulfonylurea to 50% current dose to reduce the risk of hypoglycemia unless baseline glucose is significantly elevated at initiation of liraglutide.
- Caution in renal and hepatic impairment; no dose adjustment of liraglutide is recommended.
- Possible increased risk of pancreatitis. If severe abdominal pain or severe nausea and vomiting, stop liraglutide and check lipase/amylase.
- Use 5 or 8 mm ultrafine pen needles with liraglutide; discard needle after each injection.
- Store liraglutide in the refrigerator until opened. After first use, may be stored at room temperature (59°F to 86°F) or in the refrigerator. Discard 30 days after first use.
- Nausea is common when starting liraglutide. If severe nausea, stop liraglutide. If mild nausea, continue use as nausea diminishes over time (~4 weeks).

**Pattern Low or Elderly**
- Cut dose of sulfonylurea (eliminate if needed)

**Pattern high**
- Increase liraglutide to 1.8 mg SQ once daily* 
  *if well tolerated

**Pattern at goal**
- No change

**Evaluate glucose pattern**

**Pattern at goal**
- Consider switching to insulin

* Increase liraglutide to 1.2 mg SQ once daily after 1 week*
  *if tolerated; ↑ dose 1.8 mg if needed to achieve glycemic goals
  * Caution with use in renal/hepatic impairment

**Diabetes Type 2 Basal Insulin Guideline**
For all Medicines RN / MD should check medication specific contraindications before initiating.

### Table 6. Diabetes Medicines - Titration Table

<table>
<thead>
<tr>
<th>Class</th>
<th>Generic / Brand Name</th>
<th>Labs</th>
<th>Initial Dose</th>
<th>Titration Schedule</th>
<th>RN Monitoring Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BIGUANIDES</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metformin 500mg (Glucophage)</td>
<td>Renal, CBC (order comp. met. panel) at baseline and at least annually; for patients susceptible to renal impairment, monitor more frequently (Q3-Q6 months)</td>
<td>500 mg once daily or bid</td>
<td>Increase by 500 mg weekly to Max dose: 1000 mg bid or 2000 mg/day</td>
<td>▪ Take with food to decrease GI upset (i.e. breakfast and dinner). This intolerance may improve over time.</td>
<td></td>
</tr>
<tr>
<td>Metformin 850mg (Glucophage)</td>
<td></td>
<td>850 mg daily</td>
<td>Increase by 850 mg every other week given bid Max dose: 2550 mg daily (3 tablets)</td>
<td>▪ Recent studies suggest vitamin B12 and/or folic acid deficiency with metformin use; supplementation may be required.</td>
<td></td>
</tr>
<tr>
<td>Metformin SR (Glucophage XR)</td>
<td></td>
<td>500 mg qPM</td>
<td>Increase by 500 mg weekly to maximum of 2000 mg daily</td>
<td>▪ Patient may experience a metallic taste.</td>
<td></td>
</tr>
</tbody>
</table>

| BIGUANIDES |                        |      |                       |                                              |                              |
| Fortamet |                             | 1000 mg qPM | Increase by 500 mg weekly Max dose: 2500 mg qPM | ▪ Start with 500 mg tablets, be alert of the number of tablets patient taking daily and change to 1,000 mg tablets as needed |
| Glumetza |                             | 1000 mg qPM | Increase by 500 mg weekly; Max dose: 2000 mg qPM | ▪ No hypoglycemia, prevents weight gain |
| *Used after GI intolerance to Metformin |                             | | | ▪ Max PG effect at 3-4 weeks |

| SULFONYLUREAS |                        |      |                       |                                              |                              |
| Glyburide Regular tabs (Micronase, Diabeta) | Renal and ALT (order comp. met. panel) at baseline and annually | 2.5 – 5 mg/day | Increase by increments no greater than 2.5 mg weekly based on patients FPG response. If dose >10mg/day, consider BID dosing. Max dose: 20 mg/day | ▪ Take 30 minutes prior to meals at same time each day; give XL tablets with meal (i.e. breakfast) |
| *Regular glyburide tablets are not interchangeable with micronized tablets |                             | | | ▪ Monitor for hypoglycemia (particularly in elderly and renal impairment) and weight gain |
| |                             | | | ▪ Glipizide may be preferred in older patient with mildly compromised renal function |
| |                             | | | ▪ Weight gain (~ 2kg) common following initiation of treatment |
| |                             | | | ▪ Max PG at 5-7 days |

▲ Primary drug of choice
<table>
<thead>
<tr>
<th>Drug</th>
<th>Initial Dose and Increment</th>
<th>Contraindications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glipizide (Glucotrol) ▲</td>
<td>5 mg daily with breakfast, increase by 2.5 – 5 mg weekly until FPG goal or maximum of 40 mg (total daily dose) or 15 mg (single dose). Doses greater than 15mg should be divided bid. For elderly or patients with mild to moderate renal dysfunction, initial dose and dose increases should be 50% of those above.</td>
<td>▪ DKA, Hypersensitivity (rare)</td>
</tr>
<tr>
<td>Glipizide XL (Glucotrol XL)</td>
<td>5 mg daily with breakfast or the first main meal, increase by 2.5 – 5 mg weekly until FPG goal or maximum of 20mg daily. For elderly or patients with mild to moderate renal dysfunction initial dose and dose increments should be 50% of those above.</td>
<td>▪ Renal or hepatic dysfunction, escalate to MD as needed ▪ Hypoglycemia: caution with decreased calorie intake, prolonged exercise, alcohol, or if used with other glucose-lowering drugs (e.g. insulin) ▪ Do not use concurrently with non-SFU secreteagogues (repaglinide/nateglinide) due to similar effect ▪ Sulfonamide allergy: potential for cross-reaction ▪ G6PD deficiency: refer to MD ▪ Glipizide not recommended with ClCr &lt; 10 ml/min ▪ Glyburide not recommended with ClCr ≤ 50mL/min or renal failure</td>
</tr>
<tr>
<td>Glimepiride (Amaryl)</td>
<td>Start 1 mg or 2 mg once daily, with breakfast or the first main meal, once 2 mg reached, increase by 2 mg every 1-2 weeks until FPG goal reached. Max Dose: 8 mg once daily</td>
<td>▪</td>
</tr>
</tbody>
</table>

▲ Primary drug of choice
### Pioglitazone (Actos)

- **ALT at baseline, and periodically (at least (annually) thereafter**
- **Cardiac status**
  - EF if available or clinical symptoms of HF
- **Routine ophthalmic exams**
- **Assess liver function if:**
  - Patient complains of nausea, vomiting, abdominal pain, and dark urine.

- **Increase by 15 mg every 4 weeks until maximum of 45 mg daily if FPG not < 130 mg/dl**
- **May take with or without food**
- **Favorable lipid effects, no hypoglycemia**
- **Weight gain: dose-related**
- **Fluid retention: may cause significant peripheral edema**
  - More prevalent when utilized with insulin. Adding spironolactone may minimize this.
- **Max effect in 6 – 12 weeks.**

**Black Box Warning:**
- **TZDs can cause or exacerbate CHF in some patients. Not recommended for use with HF sx.**
  - After initiation and dose increases monitor patients for S/Sx of heart failure (incl. dyspnea, edema, and excessive, rapid weight gain)

**Contraindications:**
- **Heart Failure Class III or IV (initiation of treatment)**
- **ALT > 2.5x ULN**

**Caution:**
- **May increase risk of fractures of long bones, especially in women**
- **Fluid retention may lead or exacerbate heart failure or macular edema (if so, drug should be stopped).**
- **Elevated AST or ALT**
- **Potential for drug interactions (e.g. bcp)**
- **May decrease Hgb/Hct – cautious use in patients with concurrent anemia**
- **Fluid retention may lead to or exacerbate heart failure or macular edema; stop drug**

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### Glyburide/Metformin (Glucovance) ▲ (generic)

- **Baseline and ongoing monitoring parameters should be consistent with individual products**
- **1.25 mg/250 mg**
- **2.5 mg/500 mg**
- **5 mg/500 mg**

**Combination products are difficult to utilize for dose titration as they do not allow for flexibility of increasing individual agents.**

**Utilize combination products for patients on stable dose of multiple medications.**

**When patients are stable on these classes of medications there may be a potential for cost savings (especially in regards to co-pays) and improved adherence with combination agents. Assess and change patients as needed**

**Monitoring and Contraindication information for individual products should be reviewed.***

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**▲ Primary drug of choice**
<table>
<thead>
<tr>
<th>ALTERNATIVES</th>
<th>MEGLITINIDES</th>
<th>ALPHA GLUCOSIDASE INHIBITORS</th>
<th>DPP-4 INHIBITOR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nateglinide (Starlix)</td>
<td>Renal and ALT (order comp. met. panel) at baseline and annually</td>
<td>Renal at baseline and annually</td>
<td>Renal at baseline and annually</td>
</tr>
<tr>
<td>120 mg TID prior to meals *If close to goal, may start at 60 mg tid</td>
<td>25 mg tid with first bite of each main meal</td>
<td>100 mg daily</td>
<td></td>
</tr>
<tr>
<td>Max Dose: 360 mg/day</td>
<td>Titrate by 25 mg per dose every 4-8 weeks intervals until 1 hour post-prandial at goal or maximum of 100 mg tid (if &gt; 60 kg) or 50 mg TID if &lt; 60 kg)</td>
<td>No titration required</td>
<td></td>
</tr>
<tr>
<td>Can double pre-prandial dose every week until FPG goals reached or maximum of 4 mg</td>
<td></td>
<td>Mild to moderate renal dysfunction (Clcr &gt; 30 ml/min and &lt;50 ml/min): decrease dose to 50 mg per day.</td>
<td></td>
</tr>
<tr>
<td>Weight</td>
<td>25 mg tid with first bite of each main meal</td>
<td>Severe renal dysfunction or ESRD: decrease dose to 25 mg/d</td>
<td></td>
</tr>
<tr>
<td>Repaglinide (Prandin)</td>
<td>Weight</td>
<td></td>
<td>Saxagliptin (Onglyza)</td>
</tr>
<tr>
<td>0.5 mg tid if A1C &lt; 8% or untreated</td>
<td>25 mg tid with first bite of each main meal</td>
<td>Renal at baseline and annually</td>
<td>Renal at baseline and annually</td>
</tr>
<tr>
<td>1 mg – 2 mg tid if previously treated or A1C &gt; 8%</td>
<td>Titrate by 25 mg per dose every 4-8 weeks intervals until 1 hour post-prandial at goal or maximum of 100 mg tid</td>
<td>2.5 – 5 mg once daily</td>
<td>2.5 – 5 mg once daily</td>
</tr>
<tr>
<td>Max Dose: 360 mg/day</td>
<td></td>
<td>*Reduce dose if administered with strong CYP3A4/5 inhibitors</td>
<td>*Reduce dose if administered with strong CYP3A4/5 inhibitors</td>
</tr>
<tr>
<td>Can double pre-prandial dose every week until FPG goals reached or maximum of 4 mg</td>
<td></td>
<td>Clcr &lt; 50 ml/min: 2.5 mg/day</td>
<td>Clcr &lt; 50 ml/min: 2.5 mg/day</td>
</tr>
<tr>
<td>Weight gain</td>
<td>Weight gain</td>
<td></td>
<td>Weight gain</td>
</tr>
<tr>
<td>Lower risk of hypoglycemia than SFUs</td>
<td>Lower risk of hypoglycemia than SFUs</td>
<td></td>
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</tr>
<tr>
<td>Contraindications</td>
<td>Contraindications:</td>
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<td>Contraindications:</td>
</tr>
<tr>
<td>DKA, hypersensitivity reactions (rare)</td>
<td>Bowel disease, DKA, cirrhosis (Acarbose only), GI disease</td>
<td>Hypersensitivity e.g. anaphylaxis, angioedema (Sitagliptin only)</td>
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</tr>
<tr>
<td>Caution:</td>
<td>Warning:</td>
<td>Warning:</td>
<td>Warning:</td>
</tr>
<tr>
<td>Renal or hepatic impairment</td>
<td>Use not recommended with significant impairment (SCr &gt; 2 mg/dL)</td>
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</tr>
<tr>
<td>May cause hypoglycemia</td>
<td>Dose-related, transient increase in AST/ALT</td>
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<td>Dose-related, transient increase in AST/ALT</td>
</tr>
<tr>
<td></td>
<td>May be taken with or without food</td>
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</tr>
<tr>
<td></td>
<td>Cases of acute pancreatitis reported with use; discontinue if suspected (Sitagliptin only)</td>
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<td>Cases of acute pancreatitis reported with use; discontinue if suspected (Sitagliptin only)</td>
</tr>
<tr>
<td></td>
<td>No hypoglycemia or weight gain</td>
<td>No hypoglycemia or weight gain</td>
<td>No hypoglycemia or weight gain</td>
</tr>
<tr>
<td></td>
<td>PG effect within 1-2 weeks of initiation</td>
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</tr>
<tr>
<td></td>
<td>Common AEs: Headache, URI and/or UTI</td>
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</tbody>
</table>

▲ Primary drug of choice
<table>
<thead>
<tr>
<th>INCRETIN MIMETIC</th>
<th>Exenatide (Byetta)</th>
<th>Renal at baseline and annually</th>
<th>5 mcg SC bid</th>
<th>Increase to 10 mcg bid after 1 month if patient not at goal and tolerating GI effects</th>
</tr>
</thead>
</table>
|                  |                   | INR (with concurrent warfarin use) |             | ▪ Injectable given twice a day at any time within 1 hour before morning and evening meal or before the 2 main meals of the day, approximately 6 hours apart - Not to be taken after meals  
▪ May result in a reduction in appetite, food intake, and/or body weight  
▪ Discard pen after 30 days  
▪ Main side effects nausea/vomiting (improve over time) and weight loss  
▪ For oral medications that have a narrow therapeutic window or require rapid absorption, (e.g. contraceptives, antibiotics) patients should be advised to take those drugs at least 1h before BYETTA injection. |
|                  |                   | S/Sx of pancreatitis |             | ▪ Contraindications: Hypersensitivity; Not recommended in patients with ESRD or Cl\textsubscript{cr} <30 ml/min, gastroparesis, GI disease, DM1 or DKA |
|                  |                   |                  |             | ▪ Warnings:  
▪ Acute pancreatitis has occurred after initiation of exenatide and after dose increases - observe pts carefully for S/Sx of pancreatitis (including persistent, severe abdominal pain, sometimes radiating to the back, which may or may not be accompanied by vomiting)  
▪ Caution in patients with renal transplantation and with exenatide initiation or dose increases in patients with moderate renal impairment (Cl\textsubscript{cr} 30-50 mL/minute).  
▪ Use with caution with sulfonylurea; may increase risk of hypoglycemia – consider reducing dose of SFU  
▪ May increase INR, increase monitoring when initiating in patients on Coumadin (warfarin) |

▲ Primary drug of choice
| GLP-1 RECEPTOR AGONIST | Liraglutide (Victoza) | S/Sx pancreatitis (including persistent severe abdominal pain, sometimes radiating to the back that may or may not be accompanied by vomiting) | 0.6 mg SC once daily for 1 week | After 1 week, increase the dose to 1.2 mg SC once daily.  
If the 1.2 mg dose does not result in acceptable glycemic control, the dose can be increased to 1.8 mg SC once daily.  
Max dose: 1.8 mg/day SC | ▪ No dose adjustments in renal/hepatic impairment  
▪ Administer once daily at any time of day, independently of meals  
▪ Pen should be discarded 30 days after initial use  
▪ Use assoc. with weight loss  
▪ Common AEs: headache, nausea, and diarrhea. Nausea is most common when first starting liraglutide, but decreases over time.  
▪ Black Box Warning  
*Dose- and duration-dependent thyroid C-cell tumors have developed in animal studies with liraglutide therapy; relevance in humans unknown.*  
▪ Contraindications  
History of or family history of medullary thyroid carcinoma (MTC); patients with multiple endocrine neoplasia syndrome type 2 (MEN2)  
▪ Warnings:  
▪ Cautious use with GI disease (gastroparesis)  
▪ Acute and chronic pancreatitis: if suspected, discontinue use  
▪ Use with caution with sulfonylurea; may increase risk of hypoglycemia – consider reducing dose of SFU  
| AMYLIN ANALOG | Pramlintide (Symlin) | 60 mcg TID immediately prior to meals | Increase to 120 mcg if patient is tolerating without nausea/vomiting after 3-7 days.  
If nausea occurs at 120 mcg, decrease dose to 60 mcg TID.  
Max Dose: 120 mcg/dose SC | ▪ Reduce pre-meal insulin dose by 50%; after the maintenance dose of pramlintide is reached, adjust insulin to achieve optimal glycemic control  
▪ No dose adjustments in renal/hepatic impairment  
▪ Administer subcutaneously immediately prior to each major meal (at least 250 kcal or containing at least 30 g of carbohydrate).  
▪ Do not mix pramlintide with any type of insulin  
▪ Contraindications: Allergy, gastroparesis or hypoglycemia unawareness.  
▪ Warnings:  
▪ Potential for hypoglycemia  
▪ Nausea / vomiting primary side effect, tolerance develops over time.  
▪ Pramlintide may alter absorption of oral medicines; administer the agent at least 1 hour prior to or 2 hours after pramlintide injection  

References  
▲ Primary drug of choice