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FOR SALES TRAINING PURPOSES ONLY

Some information contained in this training program may be outside the approved prescribing information for *AVANDIA or AVANDAMET*. Please consult the Prescribing Information for both *AVANDIA* and *AVANDAMET*. For additional information call the drug information department at 1-888-825-5249 {GSK, is this the right number}

Link to *AVANDIA* PI **Link to *AVANDAMET* PI**

IM01010
Overview

NARRATIVE	ON-SCREEN TEXT/GRAPHICS	DIRECTIONS
Welcome to the *AVANDIA* Family e-Library!	Welcome to the *AVANDIA* Family e-Library! The goal of the *AVANDIA* Family e-Library is to provide an avenue for continued learning for GSK sales representatives and account managers. This electronic resource center offers a comprehensive collection of educational material covering various topics that help you further your knowledge of type 2 diabetes mellitus. **Robot: Follow me to the next few screens as I walk you through some important features of the program.** **Click the <Next> button below to continue.**	Text appears with screen. Robot comes in and reads last sentence

Question	On-Screen Answer	Robot Answer
How long is each module? IM01020	The length of the module depends on the topics and relevant material that must be covered. However, typically, a module can be completed within anywhere from 20 to 40 minutes.	You won't be bored, I promise!
What are the target topic areas covered in this program? IM01030	The *AVANDIA* Family e-Library offers a comprehensive collection of educational material covering various topics including those listed below: ▪ *AVANDIA* and *AVANDAMET* Products ▪ Competitive Products ▪ Disease States / Patient Populations ▪ Customers ▪ Health Care Environment	The e-Library can help you with numerous topics.
Am I required to complete the entire module? IM01040	Each module is broken down into multiple lessons, which are listed on the Main Menu. Each lesson consists of learning objectives, training material, and a quick progress check. I highly encourage you to review all pages of content and complete the progress check presented at the end of each lesson. <**Click Here for More Information**> Content that appears within tip Box: Tip boxes appear on select pages, providing you with valuable "Important to Know" information. You can close the Tip Box by clicking the <Minimize> button (see above). To open the pop-up again, click on <Maximize>.	Wanna try it? Go ahead, don't be afraid.
Are there any progress checks along the way? IM01050	Yes. A progress check (typically consisting of 2-5 questions) appears at the end of each lesson. Each progress check gives you the opportunity to assess your knowledge. Completion of the progress checks is not mandatory.	Now don't you wanna make sure that you know the material before you take the Final Assessment?

Can I print the material? IM01060	For your convenience, a printable Program Summary is provided for each module. You can access this item from the Main Menu. Content appears in Adobe Acrobat and may be viewed on screen or printed. The Program Summary is for sales training purposes only and should not be distributed to customers.	You can optionally print the Program Summary if you want something to remember me by!
Am I required to complete the Final Assessment? IM01070	In order to obtain credit for the module, you must complete the Final Assessment. The Final Assessment typically consists of 10 questions in multiple choice and true & false formats. You must achieve a passing grade of 80% to pass the course.	Prove to me how good you are!
Can I distribute course material to customers? IM01080	The materials in the e-Library are provided for GSK field personnel use and for sales training purposes only. Not to be distributed to healthcare professionals.	No way! My e-Library consists of material for training purposes only.
Is there anything else I may need help with? IM01085	Periodically throughout the program, you may see a blinking "Competitive Connection" box at the bottom of your screen. Click on it to receive useful data regarding *AVANDIA.* Also, roll your mouse over any underlined items you may notice. They will also lead you to more important information such as definitions or footnotes. **Competitive Connection:** Positive attributes of *AVANDIA* will be listed here. **Footnote Popup** Be sure to check all footnotes.	Click the <Competitive Connection> box below to see how it works, and be sure to check the footnote text!

IM01090
Overview

NARRATIVE	ON-SCREEN TEXT/GRAPHICS	DIRECTIONS
Click the <Return> button to go back to the Main Menu.	I hope this overview has given you a better understanding of the *AVANDIA* e-Library. Click the <Return> button to go back to the Main Menu.	You can close this screen at any time by clicking <Close>, located on the upper-right corner of the screen. Alternatively, you can click on the <Return> button below, when presented at the end of each chapter. I'll pop in from time to time to point out some important information that needs special attention. See you soon!

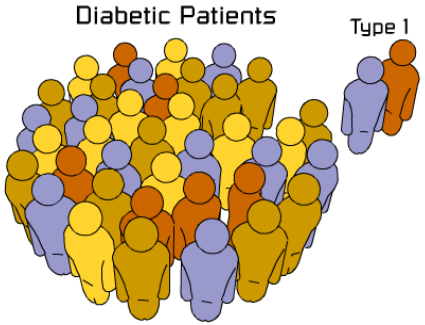
IM02010

Core Defects of Type 2 Diabetes

NARRATIVE	ON-SCREEN TEXT/GRAPHICS	DIRECTIONS
The following are the learning objectives for this section:	**Learning Objectives** • Compare the differences between type 1 and type 2 diabetes • Describe the role of insulin in glucose control • Understand the importance of targeting core defects of type 2 diabetes: o Insulin resistance o Beta-cell impairment	Text appears with screen.

IM02020
Core defects of Type 2 Diabetes

NARRATIVE	ON-SCREEN TEXT/GRAPHICS	DIRECTIONS
Approximately 17 million people in the United States have diabetes. 10% of these patients have type 1 and approximately 90% have type 2 diabetes. (http://www.cdc.gov/diabetes/pubs/estimates.htm) (Merck Manual, p1107–1109)	**Diabetes Mellitus – Overview** **Type 1 Diabetes** • Up to 10% of all diabetes cases • Typically occurs during childhood or adolescence • Absolute endogenous* insulin deficiency due to acute beta-cell failure (autoimmune) • Exogenous* insulin therapy is required to control blood glucose levels **Type 2 Diabetes** • Approximately 90% of all diabetes cases • Typically occurs in adulthood, but increasingly in childhood and adolescence • Commonly associated with obesity (Merck Manual) • A complex disease process of increased insulin resistance at the target level eventually leading to progressive beta-cell failure • Historically, as insulin resistance worsens, greater demand is placed on the beta-cells, requiring patients to become dependent on insulin therapy **Footnote Popup** ***Endogenous insulin—**Insulin originating inside the body, produced by the pancreas. ***Exogenous insulin—** Insulin originating outside the body introduced by insulin therapy.	Text appears with screen. Show a graphic of % of people with type 1 and type 2. Links to definitions of endogenous insulin and exogenous insulin.

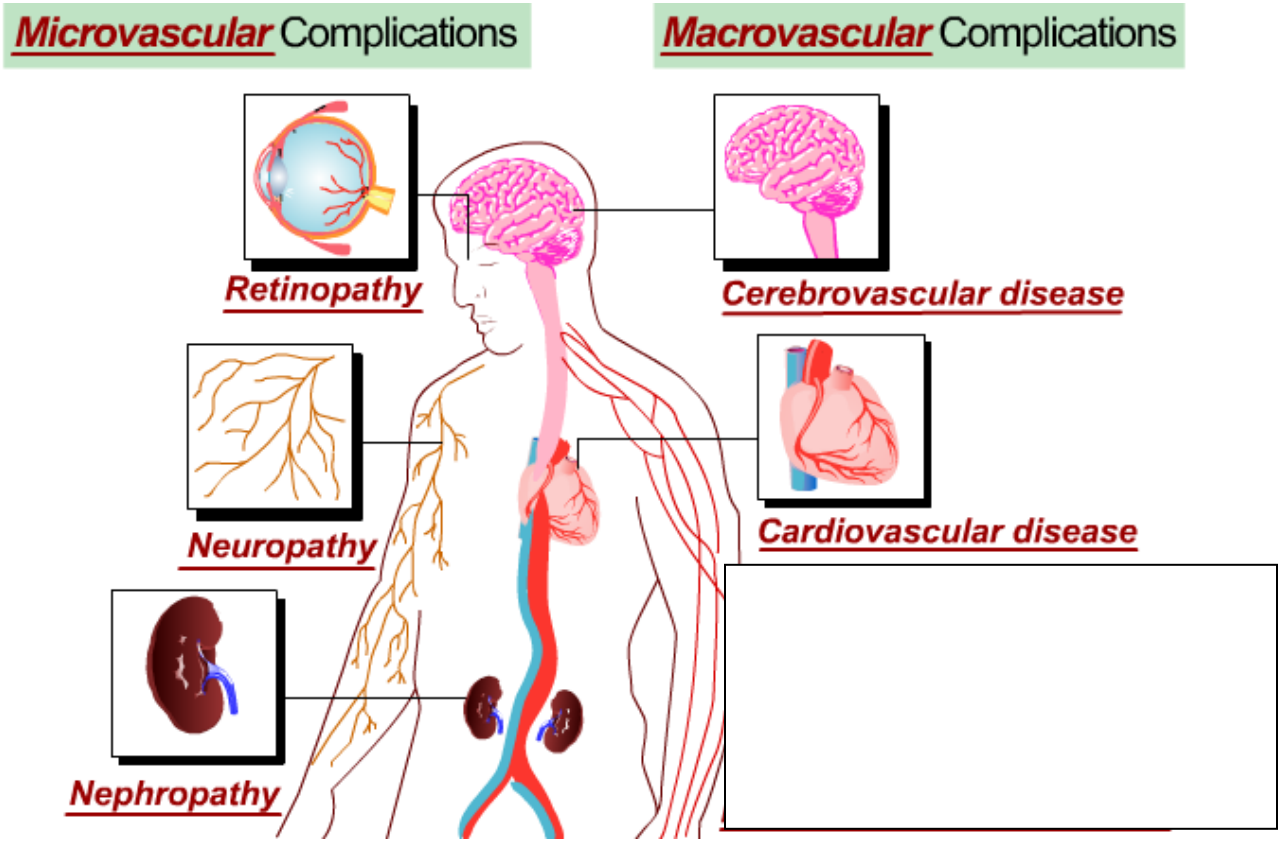


IM02030

Core defects of Type 2 Diabetes

NARRATIVE	ON-SCREEN TEXT/GRAPHICS	DIRECTIONS
Diabetes mellitus is a metabolic disorder that can lead to a range of serious complications including those listed here. Roll over each item for details. *(Merck Manual, p1106–1107),*	**Complications of Diabetes** Uncontrolled diabetes can lead to serious and potentially life-threatening complications. ***Microvascular*** • ***Retinopathy*** • ***Neuropathy*** • ***Nephropathy*** ***Macrovascular*** • ***Cardiovascular disease*** • ***Cerebrovascular disease*** • According to the United Kingdom prospective Diabetes Study (UKPDS), achieving goal is essential since every 1% increase above goal elevates the risk of diabetic complications, including: o 21% increase in any diabetes-related endpoint o 14% increase in risk of myocardial infarction (MI) o 12% increase in risk of stroke o 37% increase in risk of microvascular complications • Medical expenses for people with diabetes are 5 times than of people without diabetes. (Diabetes Care, Economic cost of diabetes in the US 2002, p917) Roll over each item for details.	Show a human body with links to various organs impacted by the complication.

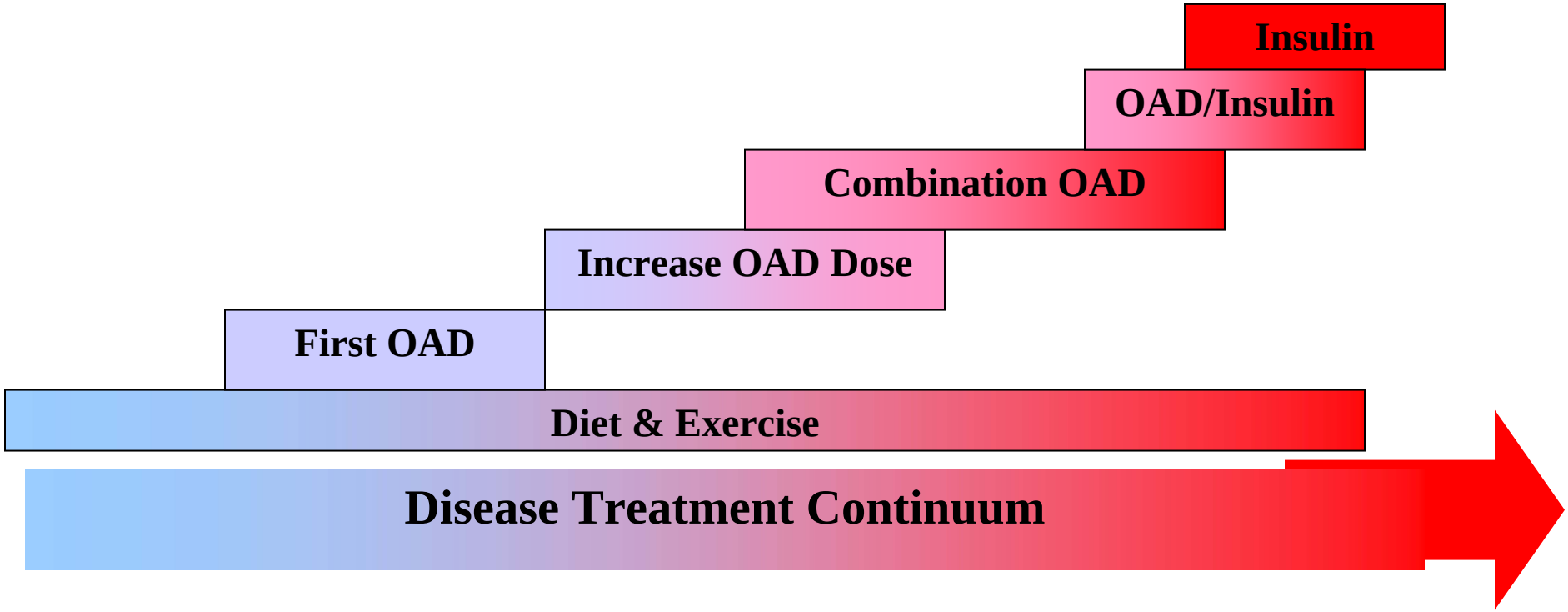
Microvascular—Affecting the smallest blood vessels (arterioles and capillaries); in diabetes mellitus, often refers to complications such as retinopathy, neuropathy, and nephropathy
Retinopathy—Damage to the retina, which translates visual objects into neural signals; microvascular complication of diabetes
Neuropathy—Nerve damage; microvascular complication of diabetes
Nephropathy—Kidney damage; microvascular complication of diabetes
Macrovascular—Affecting the medium and large vessels; in diabetes mellitus, refers to complications such as cardiovascular disease, cerebrovascular disease, and peripheral vascular disease
Cardiovascular disease—Disease affecting the heart; macrovascular complication of diabetes
Cerebrovascular disease—Disease affecting the blood vessels that supply the brain with blood; macrovascular complication of diabetes



IM02040

Core defects of Type 2 Diabetes

NARRATIVE	ON-SCREEN TEXT/GRAPHICS	DIRECTIONS
The treatment continuum for type 2 diabetes starts with diet and exercise, then progresses to OAD monotherapy, combination OAD therapy, and ultimately to insulin therapy over time.	**Understanding Type 2 Diabetes** • Type 2 diabetes is a progressive and incurable disease • Patients slowly become unable to produce or use insulin to control glucose levels as the body becomes more insulin resistant • Treatment of type 2 diabetes is often advanced with progression of the disease along the following continuum: o Diet and exercise o Oral anti-diabetic drugs (OADs) o Increase OAD dose o Combination OAD o OAD combination with insulin o Insulin Diet and exercise are ongoing components of the disease treatment continuum.	Text appears with screen. Show a graphic of the continuum.

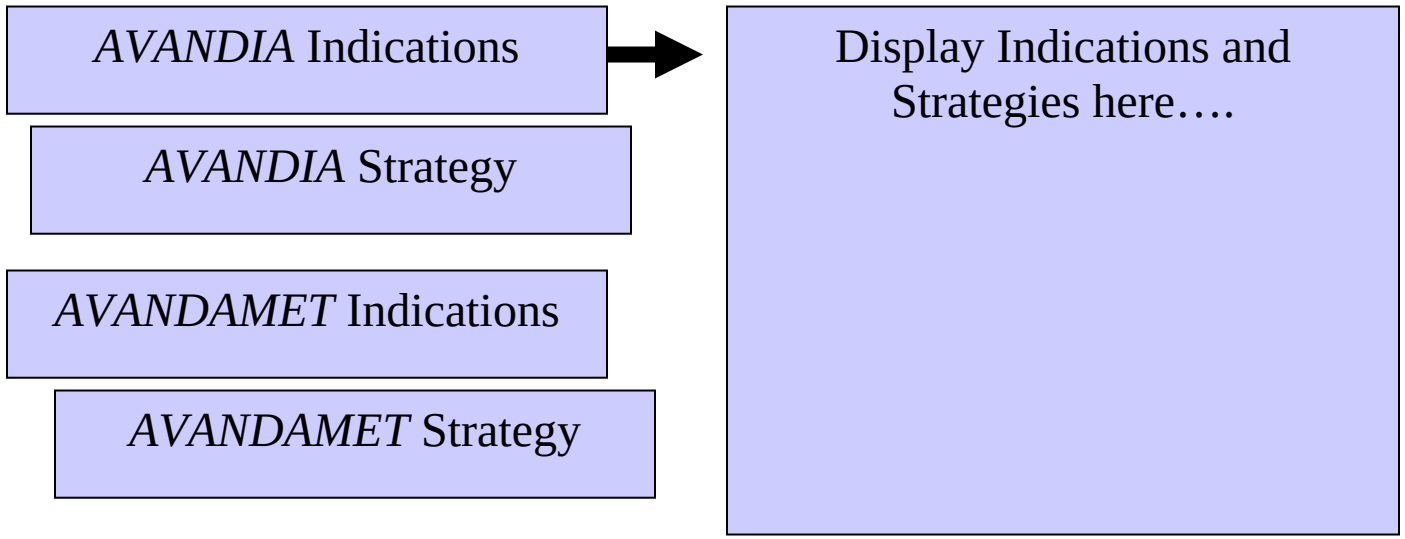


IM02050

Core defects of Type 2 Diabetes

NARRATIVE	ON-SCREEN TEXT/GRAPHICS	DIRECTIONS
AVANDIA and *AVANDAMET* target core defects in type 2 diabetes providing improvements in insulin resistance and estimates of beta-cell function, which may help to slow the progression of this chronic disease. Click each item to view more details.	**Targeting Core Defects of Type 2 Diabetes** • *AVANDIA* Indications: o Adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes mellitus o Use as monotherapy, and in combination with a sulfonylurea, metformin, or insulin when diet, exercise, and a single agent do not result in adequate glycemic control ***AVANDIA* is now indicated for use in combination with insulin therapy.** • *AVANDIA* Strategy: o Recently diagnosed patients with type 2 diabetes who are not at goal (HbA_{1c} <7%) with diet and exercise o Patients with type 2 diabetes who are not at goal (HbA_{1c} <7%) with a sulfonylurea o Patients with type 2 diabetes who are on insulin • *AVANDAMET* Indications: o Adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes who are already treated with combination rosiglitazone and metformin or who are not adequately controlled on metformin alone • *AVANDAMET* Strategy: o Patients with type 2 diabetes who are not at goal (HbA_{1c} <7%) with metformin Click each item to view more details. **Important to Know:**	Text appears with screen. User clicks on each button to reveal.

	• Among adults with diagnosed diabetes, about 11% take both insulin and oral medications, 22% take insulin only, 49% take oral medications only, and 17% do not take either insulin or oral medications. (National Diabetes Fact Sheet, 2002) • Physicians often administer Insulin (for a short period of time) to manage acute episodes of elevated blood glucose levels (>250 mg/dl). Patients are usually titrated off insulin once glucose levels drop down to a range where they can be managed by oral therapy.	

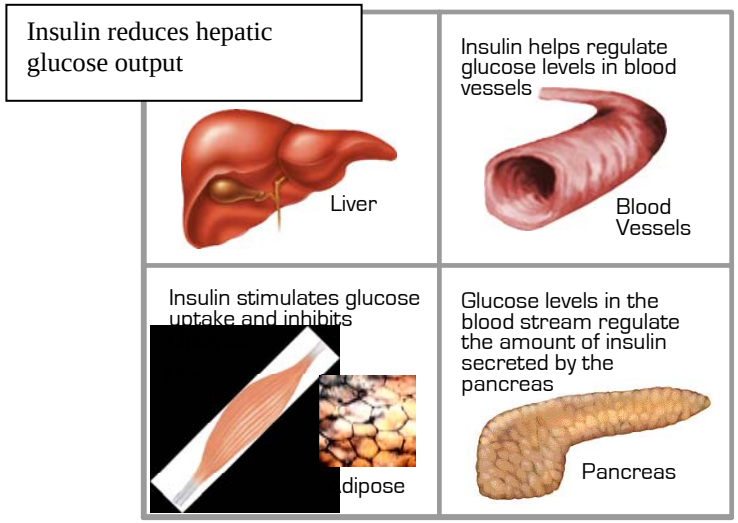


Note to Tricore: If needed, You can create 2 buttons, <Avandia> and <Avandamet>. Then the text box on the right will display both Indications and Strategies.

IM02060

Core defects of Type 2 Diabetes

NARRATIVE	ON-SCREEN TEXT/GRAPHICS	DIRECTIONS
Insulin plays an important role in glucose control. Insulin enables the body to maintain proper glucose balance. *(Merck Manual, p1108–1109)*	**Role of Insulin in Glucose Control** Insulin enables the body to maintain proper glucose balance. • Reduces hepatic glucose output • Stimulates glucose uptake in tissues • Inhibits lipolysis (breakdown of triglycerides into glycerol and free fatty acids) **Rollover each item for description** **Important to Know:** Glucose levels in the blood stream help regulate the amount of insulin secreted by the beta-cells in the pancreas.	Text appears with screen. Show a graphic of the liver, skeletal muscle, adipose tissue, blood vessels and the pancreas with appropriate labels to indicate role of insulin on each.



IM02070

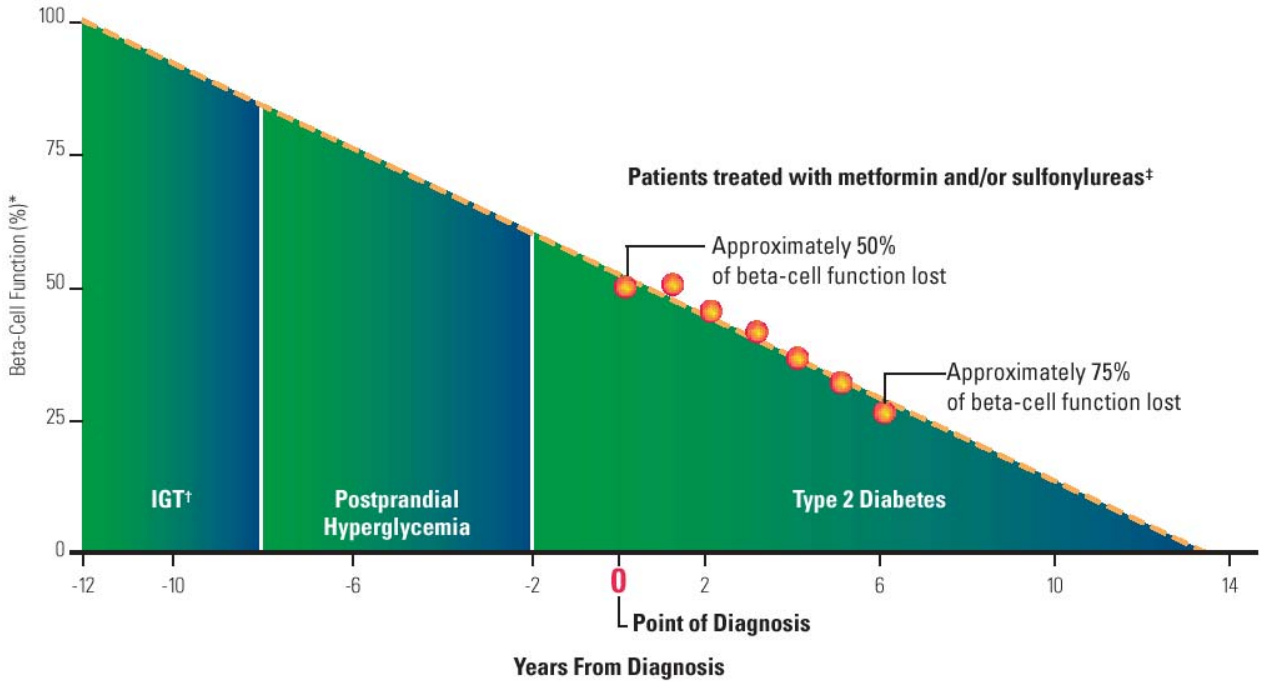
Core defects of Type 2 Diabetes

NARRATIVE	ON-SCREEN TEXT/GRAPHICS	DIRECTIONS
Insulin facilitates glucose uptake in tissues. In type 2 diabetes, insulin resistance leads to an accumulation of insulin and increased circulating glucose. Click each button for more information. Under normal conditions, insulin stimulates the uptake of glucose into tissues by binding with insulin receptors on the surface of cells. With insulin resistance, the physiologic action of insulin receptors is impaired and the number of available insulin receptors is reduced causing both insulin and glucose to build up in the blood stream. *Kahn SE. J Clin Endocrionol Metab 2001;86(9):4047-4058*	**Insulin Resistance** **Normal Physiology** • Insulin binds to receptors on the cell surfaces to facilitate glucose transport **Insulin Resistance** • Impaired physiologic action of insulin receptors and possible decrease in the number of insulin receptors (**down regulation***) leads to the accumulation of insulin and increased circulating glucose • Insulin resistance is believed to precede beta-cell impairment in type 2 diabetes * **Down-Regulation**: A decrease in the number of receptors as a regulatory mechanism to compensate for their increased activation. **Competitive Connection:** • Impairment of insulin secretion and/or insulin sensitivity may result in hyperglycemia • In the management of diabetes, it is critical to target core defects of type 2 diabetes: Insulin resistance and beta-cell impairment Click each button for more information.	Text appears with screen. **Normal Physiology** Show animation of insulin binding to receptor and facilitating the uptake of glucose. **Insulin Resistance** Show animation of insulin not being able to bind to insulin receptors and levels of insulin and glucose increase in the blood stream.

IM02080
Core defects of Type 2 Diabetes

NARRATIVE	ON-SCREEN TEXT/GRAPHICS	DIRECTIONS
As insulin resistance worsens, greater demand is placed on the beta-cells and the pancreas compensates by secreting more insulin. Over time, the beta cells loose their ability to secrete insulin. (Marks, medforum.nl) (Lebovitz, p139–153)	**Beta-cell Impairment** **Beta-cell Impairment** • As insulin resistance worsens, beta-cells produce more insulin • The beta-cells become overworked • The beta-cells' ability to produce insulin declines over time • The decline in beta-cell function leads to initiation of insulin therapy **Competitive Connection:** • *AVANDIA* may delay the progression of type 2 diabetes by targeting insulin resistance and improving estimates of beta-cell function • In long-term extension studies, *AVANDIA* is the only TZD with durability as monotherapy for up to 3½ years* **Footnote Popup** *(goes with Competitive Connection)* *Patients who received AVANDIA 8 mg QD and 4 mg BID for at least 42 months during 2 double-blind, 26-week, placebo-controlled trials and their open-label extensions. Results of these trials are biased because they include only those patients who elected to continue on AVANDIA therapy for the full duration. Patients demonstrated sustained efficacy over time in these "completers."	Text appears with screen.

Percent Beta-cell Function Throughout the Stages of Type 2 Diabetes



*Dashed line shows extrapolation forward and backward from year 0 to 6 from diagnosis based on Homeostasis Model Assessment (HOMA) data from UKPDS.
†IGT = impaired glucose tolerance.
‡The data points for the of diagnosis (0) and the subsequent 6 years are taken from the obese subset of the UKPDS population and were determined by the HOMA model.

IM02090

Core defects of Type 2 Diabetes

NARRATIVE	ON-SCREEN TEXT/GRAPHICS	DIRECTIONS
Click here to start the Progress check.	**Progress Check** Robot: I'm exhausted from all of this teaching! Please help me refuel my battery by correctly answering the following questions. **Click here to start the progress check**	

IM02100

Core defects of Type 2 Diabetes

NARRATIVE	ON-SCREEN TEXT/GRAPHICS	DIRECTIONS
None	**Progress Check** 1. Which of the following does not describe type 2 diabetes? A. Accounts for approximately 90% of all diabetes cases B. Associated with obesity **C. Always requires insulin replacement therapy** D. Involves defects in insulin resistance and insulin secretion	

Incorrect Answer Feedback

Beta-cell impairment occurs slowly in type 2 diabetes, resulting in the need for insulin replacement late in the course of the disease.

IM02110
Core defects of Type 2 Diabetes

NARRATIVE	ON-SCREEN TEXT/GRAPHICS	DIRECTIONS
None	**Progress Check** 2. By which mechanism(s) does insulin help maintain blood glucose levels? A. Inhibiting lipolysis B. Stimulating glucose uptake into tissues C. Suppressing hepatic glucose secretion **D. All of the above**	

Incorrect Answer Feedback
Insulin helps maintain blood glucose levels by several mechanisms: stimulation of glucose uptake into tissues, suppression of hepatic glucose secretion, and inhibition of lipolysis.

IM02120
Core defects of Type 2 Diabetes

NARRATIVE	ON-SCREEN TEXT/GRAPHICS	DIRECTIONS
None	**Progress Check** 3. Insulin therapy is usually required by patients with type 2 diabetes late in the course of the disease. **A. True** B. False	

Incorrect Answer Feedback
Insulin therapy is required after patients have lost considerable beta-cell function and can no longer produce sufficient insulin, which occurs later in the course of type 2 diabetes.

IM02130
Core defects of Type 2 Diabetes

NARRATIVE	ON-SCREEN TEXT/GRAPHICS	DIRECTIONS
Click the <Return> button to go back to the Main Menu.	**Progress Check** Robot: Great job! You've replenished my energy! Click the <Return> button to return to the main menu.	

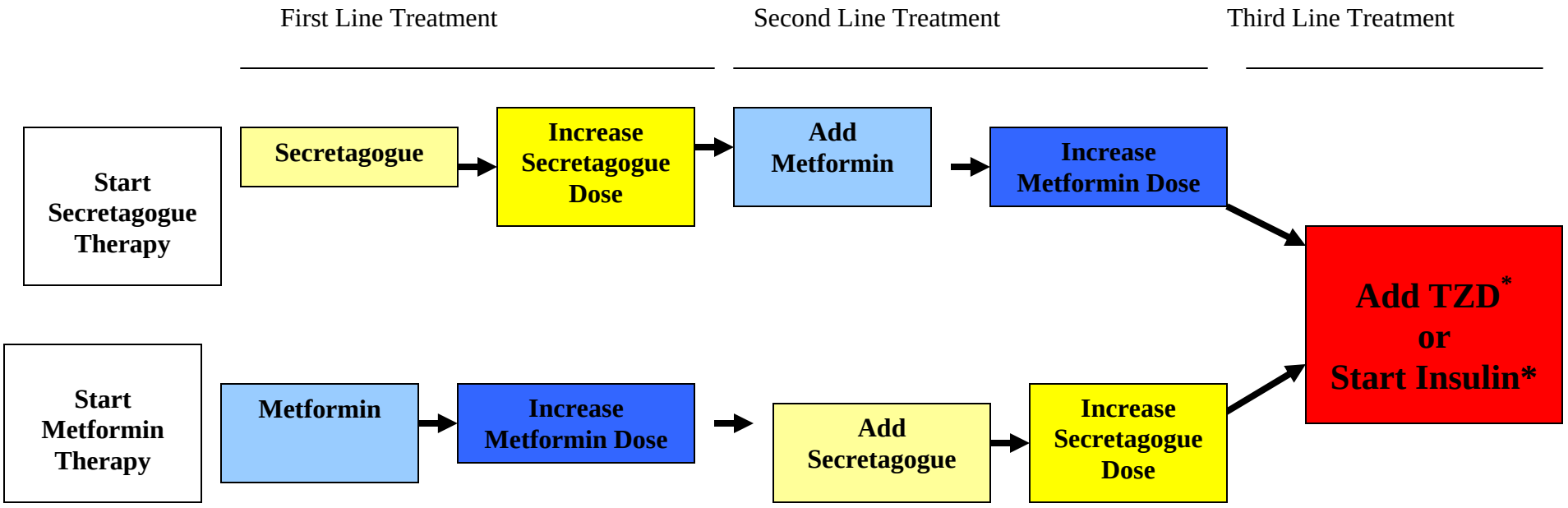
IM03010
Diabetes Treatment Matrix

NARRATIVE	ON-SCREEN TEXT/GRAPHICS	DIRECTIONS
The following are the learning objectives for this section:	**Learning Objectives** • Recognize the traditional matrix for treating type 2 diabetes • Explain the new matrix that promotes the early use of *AVANDIA* • Identify where insulin therapy fits along the treatment continuum • Reinforce the use of *AVANDIA* late in the course of type 2 diabetes in patients on insulin	Text appears with screen.

IM03020
Traditional Treatment Matrix

NARRATIVE	ON-SCREEN TEXT/GRAPHICS	DIRECTIONS
In the traditional treatment matrix, TZDs are prescribed third-line after failing secretagogue and metformin therapies. 62% of patients on OADs are not at the ADA goal of HbA_{1c} <7% Click each button to view more details.	**Traditional Treatment Matrix** **Traditional Treatment Matrix** • TZDs reserved for third-line therapy • After secretagogue and metformin failure • Late in the treatment continuum **62% of patients on OADs are not at the ADA goal of HbA_{1c} <7%** Click each button to view more details. **Footnote:** **AVANDIA* is not indicated as triple therapy.	Text appears with screen. **Traditional Treatment Matrix** Reveal graphic.

Traditional Treatment Matrix



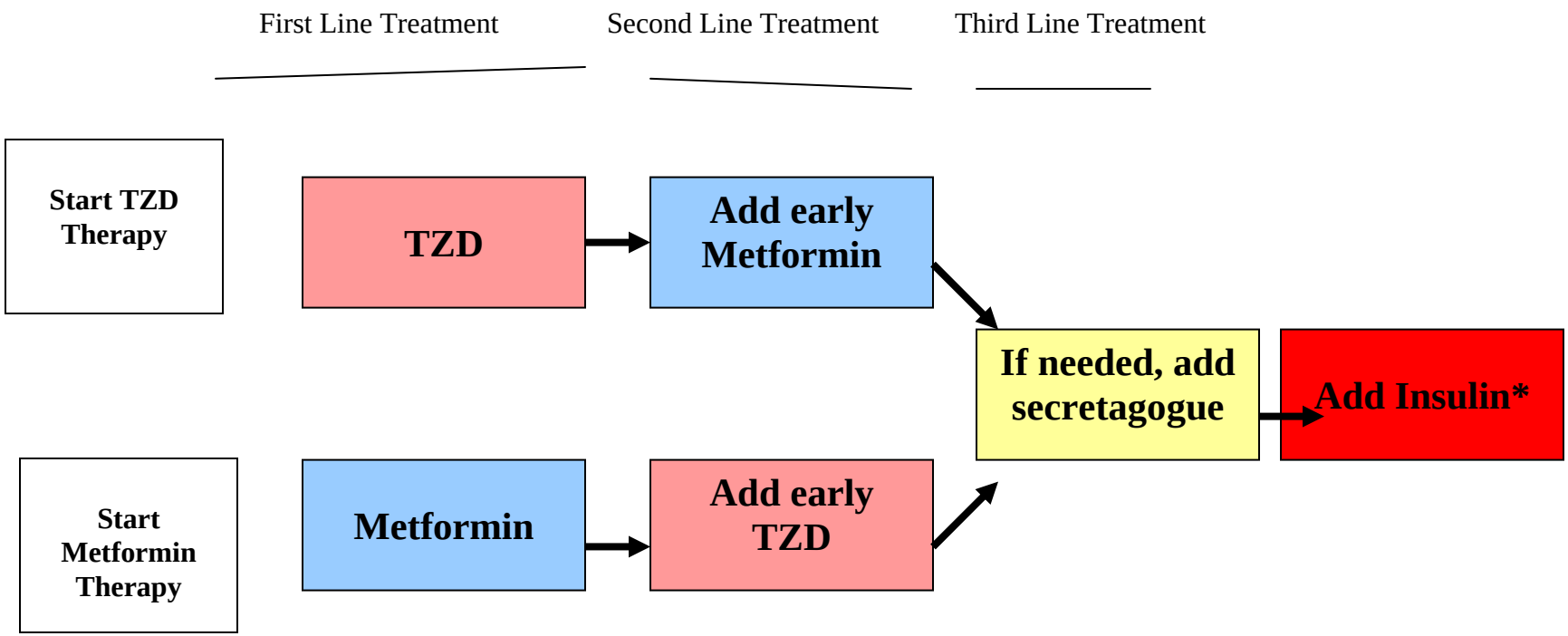
*AVANDIA is not indicated as triple therapy.

Note to Tricore: Reveal horizontally. Use Rx bottle to show Metform, and secretagogues, bigger bottle to show increased Dose. Then use Rx bottle for TZDs and a Vial for Insulin.

IM03030
Diabetes Treatment Matrix

NARRATIVE	ON-SCREEN TEXT/GRAPHICS	DIRECTIONS
In an alternative treatment matrix, TZDs may be used as monotherapy or in combination with metformin early in therapy. If needed, secretagogues are added as a third-line agent. Click each button to view more details. *{Data on File}*	**Alternative Treatment Matrix** **Alternative Treatment Matrix** • Early use of TZDs as monotherapy or in combination with other OADs • Target insulin resistance and beta-cell impairment • Help slow disease progression and the need for insulin Click each button to view more details. **Footnote: (for graphic only)** *Avandia is not indicated as triple therapy	Text appears with screen. **Alternative Treatment Matrix** Show graphic.

Alternative Treatment Matrix



(*Avandia is not indicated as triple therapy)

IM03040
Diabetes Treatment Matrix

NARRATIVE	ON-SCREEN TEXT/GRAPHICS	DIRECTIONS
Insulin is reserved for late-stage type 2 diabetes when beta-cell function fails. *AVANDIA* 8 mg/day monotherapy targets core defects of type 2 diabetes by reducing insulin resistance by 35.5% compared to placebo at 26 weeks and by improving estimates of beta-cell function by 65.7% compared to placebo at 26 weeks.	**Alternative Treatment Matrix** **OAD Treatment Rationale** • Insulin sensitizers target core defects of insulin resistance and declining beta-cell function • Secretagogues stimulate beta-cell function at the pancreas • Insulin compensates for late-stage beta-cell failure Avandia is not indicated for triple therapy. **Competitive Connection:** *AVANDIA* 8 mg/day monotherapy targets core defects of type 2 diabetes: o Reducing insulin resistance by 35.5% compared to placebo at 26 weeks o Improving estimates of beta-cell function by 65.7% compared to placebo at 26 weeks	**OAD Treatment Rational** Show graphic.

IM03050
Diabetes Treatment Matrix

NARRATIVE	ON-SCREEN TEXT/GRAPHICS	DIRECTIONS
Click here to start the Progress check.	**Progress Check** Robot: That section wasn't too bad, but I can still use some more energy. Help me refuel my battery by correctly answering the following questions. **Click here to start the progress check**	

IM03060
Diabetes Treatment Matrix

NARRATIVE	ON-SCREEN TEXT/GRAPHICS	DIRECTIONS
None	**Progress Check** 1. According to the traditional matrix, when is it thought to be appropriate to prescribe a TZD? **A. Third line, after failing secretagogue and metformin therapy** **B.** Only in combination with a Secretagogue **C.** Never in combination with metformin **D.** Only in combination with insulin	

Incorrect Answer Feedback
The traditional matrix reserved TZD therapy for late in the course of type 2 diabetes in conjunction with insulin.

IM03070
Diabetes Treatment Matrix

NARRATIVE	ON-SCREEN TEXT/GRAPHICS	DIRECTIONS
None	**Progress Check** 2. In the alternative treatment matrix, when is it appropriate to prescribe a TZD? **A.** After failing secretagogue and metformin therapy **B.** **Early as monotherapy or in combination with other OADs** **C.** Only in combination with metformin **D.** Only in combination with insulin	

Incorrect Answer Feedback
In the alternative treatment matrix indicates it is appropriate to prescribe a TZD early in the course of type 2 diabetes, either as monotherapy or in combination after sulfonylurea or metformin monotherapy fail to provide adequate glucose control.

IM03080
Diabetes Treatment Matrix

NARRATIVE	ON-SCREEN TEXT/GRAPHICS	DIRECTIONS
None	**Progress Check** 3. According to the new matrix, which antidiabetic agent should be reserved for late-stage type 2 diabetes when beta-cell function fails? **A.** **Insulin** **B.** Secretagogue **C.** Insulin sensitizer **D.** None of the above	

Incorrect Answer Feedback

Beta-cell failure results in insufficient insulin secretion by the pancreas, necessitating insulin therapy to restore endogenous insulin levels.

IM03090
Diabetes Treatment Matrix

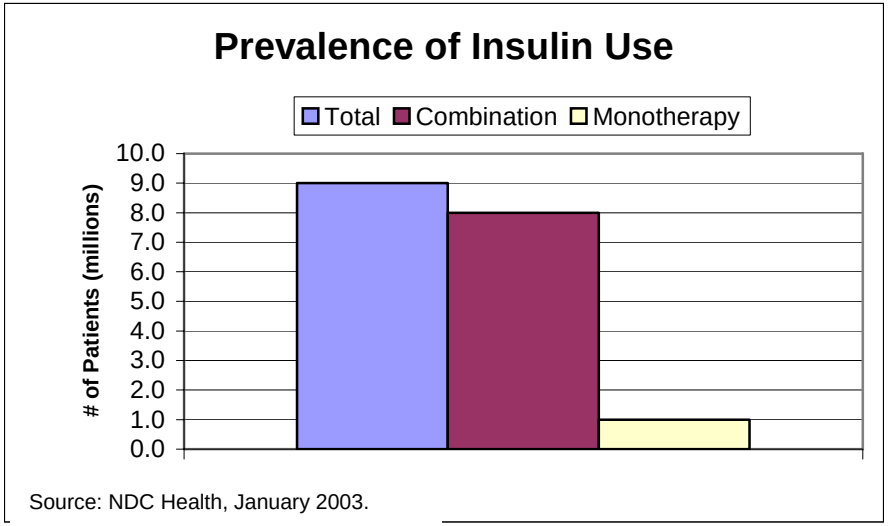
NARRATIVE	ON-SCREEN TEXT/GRAPHICS	DIRECTIONS
Click the <Return> button to go back to the Main Menu.	**Progress Check** Robot: Thanks for your help! Click the <Return> button to return to the main menu.	

IM04010
AVANDIA Use with Insulin

NARRATIVE	ON-SCREEN TEXT/GRAPHICS	DIRECTIONS
The following are the learning objectives for this section:	**Learning Objectives** • Summarize the prevalence of insulin use, including combination usage with OADs • Identify the different types of insulin preparations • List the various insulin brands and key manufacturers • Discuss the advantages and disadvantages of insulin therapy	Text appears with screen.

IM04020
AVANDIA Use with Insulin

NARRATIVE	ON-SCREEN TEXT/GRAPHICS	DIRECTIONS
Insulin is widely used by patients with diabetes, either as monotherapy or in combination with OADs.	**Prevalence of Insulin Use** ● 8.0 million patients take insulin plus an OAD ● 1.0 million patients take insulin alone (GSK assumption) ● 1.5 million patients take insulin with a TZD o 10.5% of *AVANDIA*'s prescriptions are in combination with insulin (approximately 768,206 patients) o 14.2% of Actos' prescriptions are in combination with insulin (approximately 776,121 patients) **Competitive Connection:** • Until now, Actos was the only TZD approved for use with insulin • *AVANDIA* 4 mg/day is now approved for use in combination with insulin	Text appears with screen. **Prevalence of Insulin Use** Show bar chart. **Prevalence of Insulin/OAD Use** Show bar chart.



IM04030

AVANDIA Use with Insulin

NARRATIVE	ON-SCREEN TEXT/GRAPHICS	DIRECTIONS
Insulin therapies are categorized according to their onset and duration of activity in the body. *(FDA Consumer Magazine)*	**Types of Insulin** Insulin therapy is normally the last step in the treatment continuum for type 2 diabetes.	Text appears with screen.

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Insulin Type	Onset	Peak	Duration

Rapid-Acting	10-15 minutes	30-90 minutes	3-5 hours
Short-Acting	30-60 minutes	50-120 minutes	5-8 hours
Intermediate-Acting	1-3 hours	7-15 hours	18-24 hours
Long-Acting	1-8 hours	8-12 hours	24-36 hours
Mixed Insulins	The onset, peak, and duration of action of these mixtures would reflect a composite of the intermediate and short- or rapid-acting components, with one peak of action		

IM04035
AVANDIA Use with Insulin

NARRATIVE	ON-SCREEN TEXT/GRAPHICS	DIRECTIONS
The following is a list of major insulin products by different manufacturers.	**Rapid-acting insulin** • Humalog® (*Lilly*) • Iletin® II (*Lilly*) • Novolog® (*Novo Nordisk*) **Short-acting insulin** • Humulin® R(*Lilly*) • Novolin® (*Novo Nordisk*) • Velosulin® (*Novo Nordisk*) **Intermediate-acting insulin** • Humulin® N (*Lilly*) • Humulin® L (*Lilly*) • Lente® Iletin® II (*Lilly*) • Novolin® N (*Novo Nordisk*) • Novolin® L (*Novo Nordisk*) **Long-acting insulin** • Humulin® U (*Lilly*) • Lantus® (glargine) (Aventis) (Physician's Desk Reference) (FDA Consumer Magazine) **Lantus (glargine)**—is the first FDA-approved (April 2000) recombinant human insulin analog, which works quickly (onset of action: 1 hour) to provide consistent, 24-hour coverage similar to that provided by the normal pancreas, *without* the pronounced peak in serum levels observed with human insulin. (Lantus.com) **Mixed insulins**	Text appears with screen.

	• Humulin® 50/50 (*Lilly*) • Humulin® 70/30 (*Lilly*) • Humalog® Mix 75/25™ (*Lilly*) • Humalog® 50/50 (*Lilly*) • Novolin® 70/30 (*Novo Nordisk*) • Novolog® Mix 70/30 (*Novo Nordisk*)	

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IM04040
AVANDIA Use with Insulin

NARRATIVE	ON-SCREEN TEXT/GRAPHICS	DIRECTIONS
There are advantages and disadvantages to insulin therapy.	**Advantages/Disadvantages of Insulin Therapy** **Advantages of insulin therapy** • Immediate onset of action • Experience—physicians are generally comfortable using insulin **Disadvantages of insulin therapy** • Potential hypoglycemia • Potential subcutaneous tissue infection (reactions include redness, pain, itching, hives, swelling, and inflammation) • Careful glucose monitoring and dose adjustments may be necessary in patients with renal or hepatic dysfunction • No effect on insulin resistance • Must be refrigerated	Text appears with screen.

IM04050
AVANDIA Use with Insulin

NARRATIVE	ON-SCREEN TEXT/GRAPHICS	DIRECTIONS
Click here to start the Progress check.	**Progress Check** Robot: More energy would really be great right now! Please help me refuel my battery by correctly answering the following questions. **Click here to start the progress check**	

IM04060
AVANDIA Use with Insulin

NARRATIVE	ON-SCREEN TEXT/GRAPHICS	DIRECTIONS
None	**Progress Check** 1. Insulin therapies are categorized according to their onset and duration of activity in the body. **A. True** B. False	

Incorrect Answer Feedback
There are 5 categories of insulin based on their onset and duration of activity in the body: rapid-acting, short-acting, intermediate-acting, intermediate-/short-acting, and long-acting.

IM04070
AVANDIA Use with Insulin

NARRATIVE	ON-SCREEN TEXT/GRAPHICS	DIRECTIONS
None	**Progress Check** 2. What is the brand name of the first FDA-approved recombinant human insulin analog that acts within 1 hour and provides consistent, 24-hour coverage similar to that provided by the normal pancreas? A. **Lantus** B. Lente C. Humalog D. Novolin	

Incorrect Answer Feedback
Lantus (glargine) is the first FDA-approved recombinant human insulin analog, which is unique among long-acting insulins because of its fast onset of action (within 1 hour) and consistent, 24-hour coverage.

IM04080
AVANDIA Use with Insulin

NARRATIVE	ON-SCREEN TEXT/GRAPHICS	DIRECTIONS
Click the <Return> button to go back to the Main Menu.	**Progress Check** Robot: Thanks to you, now I'm fully charged! Click the <Close> button to return to the main menu.	

IM05010
Using *AVANDIA* for Patients with Type 2 Diabetes

NARRATIVE	ON-SCREEN TEXT/GRAPHICS	DIRECTIONS
The following are the learning objectives for this section:	**Learning Objectives** • Discuss the use of *AVANDIA* early to potentially help slow the progression of type 2 diabetes • Substantiate the use of *AVANDIA* in patients with advanced type 2 diabetes who are taking insulin • Explain the pivotal clinical studies that support the use of *AVANDIA* with insulin • Describe *AVANDIA* dosing in patients who are taking insulin	Text appears with screen.

IM05020

Using AVANDIA for Patients with Type 2 Diabetes

NARRATIVE	ON-SCREEN TEXT/GRAPHICS	DIRECTIONS
The *AVANDIA* family helps patients with type 2 diabetes achieve better glycemic control throughout the disease continuum, from early to the late stages, and helps get more patients to goal.	**Choosing *AVANDIA* or *AVANDAMET*** **When to Choose *AVANDIA*** 1. Early in the course of disease (recently diagnosed type 2 diabetes) to target insulin resistance and improve estimates of beta-cell function: • ***AVANDIA monotherapy*** 2. When patients are not at goal (HbA_{1c} <7%) with sulfonylurea monotherapy: • ***AVANDIA combination therapy*** 3. Late in the course of disease when patients are on insulin: • ***AVANDIA with insulin*** **When to Choose *AVANDAMET*** **1.** When patients are not at goal (HbA_{1c} <7%) with metformin monotherapy **2.** When patients are at goal (HbA_{1c} <7%) with metformin and *AVANDIA* and can benefit from the convenience of a fixed-dose combination (NOTE: *AVANDAMET* is not indicated for use in combination with insulin) **Competitive Connection:** • *AVANDIA* is the only TZD providing proven durability as monotherapy for up to 3½ years* • *AVANDIA* and metformin in combination provides sustained additive and durable glycemic control for up to 2½ years†	Text appears with screen.

	Footnote (Competitive Connection) *Patients who received *AVANDIA* 8 mg QD and 4 mg BID for at least 42 months during 2 double-blind, 26-week, placebo-controlled trials and their open-label extensions. Results of these trials are biased because they include only those patients who elected to continue on *AVANDIA* therapy for the full duration. Patients demonstrated sustained efficacy over time in these “completers.” †Patients who received rosiglitazone 4 mg BID plus metformin 2.5 g/day for at least 30 months during a double-blind, randomized study (6 months duration) and/or its open-label extension. Results of this trial are biased because they include only those patients who elected to continue on rosiglitazone plus metformin for the full duration. Patients demonstrated sustained efficacy over time in these "completers."	

IM05030
Using AVANDIA for Patients with Type 2 Diabetes

NARRATIVE	ON-SCREEN TEXT/GRAPHICS	DIRECTIONS
In the alternative treatment matrix, early use of ***AVANDIA*** **provides clear benefits:** Reduce insulin resistance and improve estimates of beta-cell function. Approximately 40% of all patients treated with *AVANDIA* reduced their insulin dose (*AVANDIA* PI) Click each button to view more details.	**Alternate Treatment Matrix** **DO NOT CHANGE THIS SCREEN YET. CLIENT WILL GET BACK TO US ON REORGANIZATION.** ***AVANDIA*** **provides clear benefits** ■ Reduce insulin resistance ■ Improve estimates of beta-cell function **Insulin Resistance** ***AVANDIA*** 4 mg bid reduces insulin resistance by up to 35.5% compared to placebo at 26 weeks. **Beta Cell Function** ***AVANDIA*** 4 mg bid improves estimates of beta-cell function by up to 65.7% compared to placebo at 26 weeks. *AVANDIA* Monotherapy **Durability** In long-term extension studies, *AVANDIA* is the only TZD providing documented durability as monotherapy for up to 3½ years. ***AVANDIA*** **with Sulfonylureas** *AVANDIA* 2 mg bid provided enhanced glycemic control in combination with sulfonylureas at Week 26: • 1.4 % reduction in HbA_{1c} • Low incidence of hypoglycemia (4.8%) in combination with sulfonylureas (Data on file) ***AVANDIA*** **with Insulin**	Text appears with screen. Show tabs for the following links: Insulin Resistance Beta Cell Function Durability *AVANDIA* with Sulfonylureas *AVANDIA* with Insulin *AVANDIA* with metformin

	AVANDIA significantly reduces FPG and HbA_{1c} in patients who are not at goal (HbA_{1c} <7%) on insulin. (*AVANDIA* PI) • Approximately 40% of all patients treated with *AVANDIA* reduced their insulin dose (*AVANDIA* PI) **THIS TEXT WILL NEED TO SNAP INTO PLACE OR FADE IN AS IT IS DIFFERENT FROM THE REST OF THE TEXT.** ***AVANDIA* with Metformin** provides sustained glycemic control for up to 2.5 years, providing additive glycemic control of FPG and HbA_{1c} compared to metformin monotherapy.† (*AVANDAMET* Overcoming Barriers)* Click each button to view more details.	

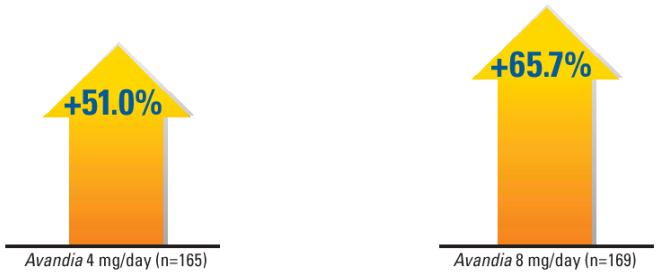
AVANDIA® Targets Core Defects of Type 2 Diabetes

▼ Improvement in insulin resistance*[1]

Insulin Resistance

*Results were measured using Homeostasis Model Assessment (HOMA) , a mathematical model that estimates insulin resistance and beta- cell function from fasting plasma insulin and glucose values. Comparison with baseline of placebo and *Avandia* 4 mg/ day (2 mg BID) and 8 mg/ day (4 mg BID) over 26 weeks in a randomized, placebo- controlled study. HOMA estimates are expressed relative to values in a lean, nondiabetic reference population aged 18 to 25 years.

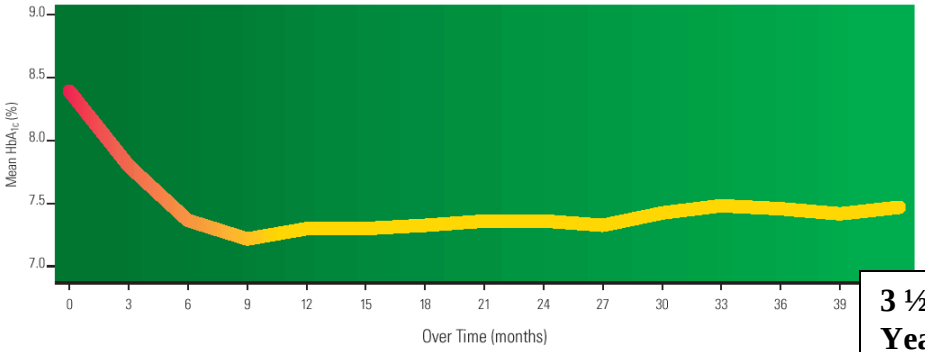
▼ Improvement in estimates of beta-cell function*[1]



Beta Cell Function

*Results were measured using Homeostasis Model Assessment (HOMA) , a mathematical model that estimates insulin resistance and beta- cell function from fasting plasma insulin and glucose values. Comparison with baseline of placebo and *Avandia* 4 mg/ day (2 mg BID) and 8 mg/ day (4 mg BID) over 26 weeks in a randomized, placebo- controlled study. HOMA estimates are expressed relative to values in a lean, nondiabetic reference population aged 18 to 25 years.

▼ **In long-term extension studies...AVANDIA® provided sustained glycemic control in HbA_{1c} up to 3½ years†1**



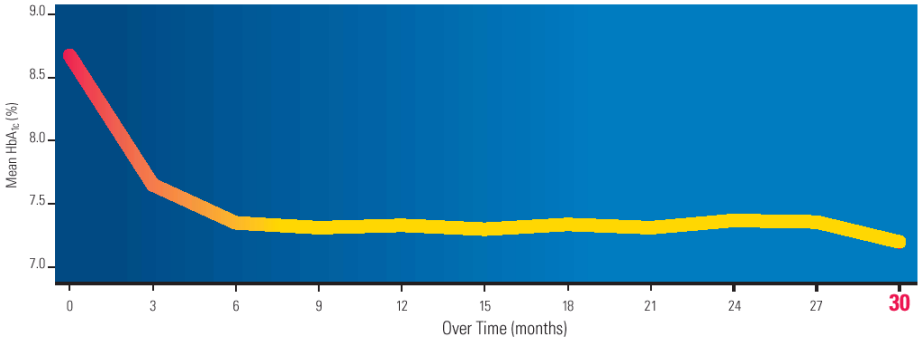
Avandia **8 mg/day (n=83) Open-label, 42-month completer analysis†**

3 ½ Years

Durability

†Patients who received *Avandia* 8 mg QD and 4 mg BID for at least 42 months during 2 double- blind, 26- week, placebo- controlled trials and their open- label extensions. Results of these trials are biased because they include only those patients who elected to continue on *Avandia* therapy for the full duration. Patients demonstrated sustained efficacy over time in these "completers."

▼ **In long-term extension studies, rosiglitazone plus metformin provided sustained glycemic control for up to 2½ years§1**



Avandia **8 mg/day plus 2.5 g/day metformin (n=88) Open-label, 30-month completer analysis§**

AVANDIA **with metformin**

§ Patients who received rosiglitazone 4 mg BID plus metformin 2.5 g/day for at least 30 months during a double-blind, randomized study (6 months duration) and/or its open-label extension. Results of this trial are biased because they include only those patients who elected to continue on rosiglitazone plus metformin for the full duration. Patients demonstrated sustained efficacy over time in these "completers."

SCREEN 05040 DELETED

IM05050
Using *AVANDIA* for Patients with Type 2 Diabetes

NARRATIVE	ON-SCREEN TEXT/GRAPHICS	DIRECTIONS
The efficacy and safety of *AVANDIA* with insulin have been evaluated in a number of studies, including those listed here. *(Use of AVANDIA letter)*	**Overview of Efficacy and Safety Studies** The efficacy and safety of *AVANDIA* in combination with insulin have been evaluated in a number of studies that included: • Two fixed-dose pivotal studies (studies 082 & 095) • One 26-week study included patients with renal failure (Study 136) • One 26-week study included patients who were well-controlled on insulin (Study 085) In the above studies, patients used various insulin formulations including regular, isophane, zinc suspension products, and Humalog® (insulin lispro [rDNA origin] injection, Eli Lilly and Company)**.** Studies have not been conducted to evaluate the use of *AVANDIA* and Lantus® (insulin glargine [rDNA origin] injection, Aventis Pharmaceuticals). **NOTE: In the *AVANDIA* PI, safety data are provided for both the 4 mg/day and 8 mg/day doses, although only *AVANDIA* 4 mg/day is approved for use in combination with insulin.**	Text appears with screen.

IM05060

Using *AVANDIA* for Patients with Type 2 Diabetes

NARRATIVE	ON-SCREEN TEXT/GRAPHICS	DIRECTIONS
In fixed dose pivotal trials, treatment with *AVANDIA* 4 mg per day in combination with insulin significantly reduced HbA_{1c} and FPG compared to baseline and insulin alone.	**Fixed Dose, Pivotal Trials** ***AVANDIA* should be dosed at 4 mg daily. Doses of *AVANDIA* greater than 4 mg daily in combination with insulin are not currently indicated.** **Study Objectives** Evaluate the efficacy and safety of *AVANDIA* in combination with insulin **Study Design** • Two randomized, 26-week, fixed dose, double-blind, placebo-controlled trials • Patients had to meet the following inclusion criteria: o Diagnosis of type 2 diabetes mellitus o Fasting C-peptide ≥ 0.4 ng/ml o HbA_{1c} ≥ 7.5% o Receiving ≥ 30 units of insulin daily at screening o FPG between 140 and 300 mg/dl during a 4-week placebo run-in period • Patient were excluded if they met any of the following criteria: o Clinically significant renal disease o Hepatic disease o Significant anemia o Severe angina, coronary insufficiency, or heart failure • Patients were randomized to receive *AVANDIA* 4 mg total daily dose, *AVANDIA* 8 mg total daily dose, or placebo in addition to the insulin injections.	Text appears with screen. Show tabs for the following links: Study Objectives Study Design Efficacy Parameters Study 082 Results Study 095 Results Safety

	• Insulin dose reductions were permitted only in response to sustained hypoglycemia **Efficacy Parameters** • The primary efficacy parameters in both studies were the mean change from baseline and placebo in HbA_{1c} at the end of 26 weeks of therapy. • Secondary parameters included: o FPG o Total daily insulin dose o Percent change in daily insulin dose **Study 082 Results** In study 082, patients treated with *AVANDIA* 2 mg BID in combination with insulin had 0.7% reduction in HbA_{1C} and 40 mg reduction in FPG as compared to placebo. ***(note: link to study results table below)*** **Study 095 Results** In study 095, patients treated with *AVANDIA* 4 mg daily in combination with insulin had 0.6% reduction in HbA_{1C} and 32 mg reduction in FPG as compared to placebo. ***(note: link to study results table below)*** **Safety** The majority of adverse events reported in the fixed-dose pivotal studies were mild to moderate and unrelated to therapy as judged by the investigators.(data on file) • Most reported adverse events were mild-to-moderate in	

	intensity and unrelated to *AVANDIA*
	• Adverse events occurring in >10% of patients included:
	  o Hypoglycemia
	  o Upper respiratory tract infection
	  o Anemia
	• The median weight gain in patients on insulin alone was 0.9 kg compared to 4.1 kg in patients who received *AVANDIA* 4 mg/day plus insulin
	• 6.8% of patients receiving *AVANDIA* in combination with insulin withdrew from the studies due to an adverse event	

Study 082 Results

The Mean (± SD) Change from Baseline in HbA_{1c}, FPG, and Insulin Dose (8 mg data was removed from chart)

	Insulin + Placebo n = 104	Insulin + *AVANDIA* 2 mg BID n = 106
HbA_{1c} (%)		
Baseline	8.9 ± 1.1*	9.1 ± 1.3
Δ from baseline	0.1 ± 1.0*	-0.6 ± 1.1†
Difference from placebo‖	-	-0.7‡
FPG (mg/dl)		
Baseline	195 ± 53.0*	212 ± 58.2
Δ from baseline	10 ± 68.1*	-42 ± 70.7†
Difference from placebo‖	-	-40‡
Insulin Dose (units)		
Baseline	70 ± 30.4	71 ± 43.8
Δ from baseline	-0.4 ± 5.6	-5 ± 14.6§
% Δ from baseline	-0.6 ± 8.24	-6 ± 15.9

n = ITT efficacy population; # doses of *AVANDIA* greater than 4 mg daily in combination with insulin are not currently indicated**;** * based on n = 103; † $p < 0.05$ vs. baseline; ‡ $p < 0.0001$ vs. insulin + placebo (adjusted mean difference); § $p \leq 0.001$ vs. insulin + placebo; || adjusted mean difference from placebo

Study 095 Results

The Mean (± SD) Change from Baseline in HbA_{1c}, FPG and Insulin Dose

	Insulin + Placebo n = 95	Insulin + *AVANDIA* 4 mg QD n = 97
HbA_{1c} (%)		
Baseline	9.1 ± 1.2	8.8 ± 1.1
Δ from baseline	0.1 ± 1.0	-0.4 ± 1.0†
Difference from placebo‖	-	-0.6‡
FPG (mg/dl)		
Baseline	203 ± 57.3	199 ± 66.3
Δ from baseline	6 ± 64.6	-25 ± 66.0†
Difference from placebo‖	-	-32‡
Insulin Dose (units)		
Baseline	65 ± 29.3	76 ± 44.8
Δ from baseline	-1 ± 8.19	-7.3 ± 16.0§
% Δ from baseline	0.2 ± 14.0	-9.1 ± 16.2

n = ITT efficacy population; # doses of *AVANDIA* greater than 4 mg daily in combination with insulin are not currently indicated**;** * based on n = 103; † $p < 0.05$ vs. baseline; ‡ $p < 0.0001$ vs. insulin + placebo (adjusted mean difference); § $p \leq 0.001$ vs. insulin + placebo; || adjusted mean difference from placebo

IM05070
Using *AVANDIA* for Patients with Type 2 Diabetes

NARRATIVE	ON-SCREEN TEXT/GRAPHICS	DIRECTIONS
In two clinical trials, hypoglycemia was the most frequently reported adverse event in patients receiving *AVANDIA* in combination with insulin. *(Use of AVANDIA letter)*	**Safety in Two Clinical Trials** • Hypoglycemia was the most frequently reported adverse event, but resulted in <1% of withdrawals (4/408) In the pivotal, fixed dose trials, edema was reported in 14.7% (60/408) of patients receiving *AVANDIA* plus insulin (4 mg/day: 12%; 8 mg/day: 17%) and 5.4% (11/203) of patients receiving insulin alone (1, 5). Reports of new onset or exacerbation of congestive heart failure occurred at rates of 1% for insulin alone, and 2% (4 mg) and 3% (8 mg) for insulin in combination with *AVANDIA*. The double-blind studies included patients with long-standing diabetes (mean, 12 years) and a high prevalence of pre-existing medical conditions including: • Peripheral neuropathy • Retinopathy • Ischemic heart disease • Vascular disease • Congestive heart failure The frequency of these concomitant illnesses was approximately twice that of the pre-marketing double-blind studies with *AVANDIA* as monotherapy and in combination with metformin or a sulfonylurea. This may help to explain the increased incidence of edema, cardiac failure, and cardiovascular adverse events observed in patients receiving *AVANDIA* and insulin combination therapy compared to insulin alone. It was not possible to determine specific risk factors that could be used to identify all patients at risk for heart failure and other cardiovascular events on combination therapy.	Text appears with screen.

IM05080

Using *AVANDIA* for Patients with Type 2 Diabetes

NARRATIVE	ON-SCREEN TEXT/GRAPHICS	DIRECTIONS
Whether prescribed as monotherapy, or in combination with metformin, a sulfonylurea, or insulin, *AVANDIA* offers outstanding dosing convenience. *(AVANDIA 3-3Lv20AVF5589.pdf)*	***AVANDIA* Dosing in Combination with Insulin** ▪ For patients stabilized on insulin, the insulin dose should be continued upon initiation of *AVANDIA*. ▪ *AVANDIA* should be dosed at 4 mg daily. Doses of *AVANDIA* greater than 4 mg daily in combination with insulin are not currently indicated. ▪ It is recommended that the insulin dose be decreased by 10% to 25% if the patient reports hypoglycemia or if FPG concentrations decrease to less than 100 mg/dl. (*AVANDIA* PI)	Text appears with screen. Picture of ***AVANDIA*** metformin and sulfonylurea, or insulin slide in.

IM05090
Using *AVANDIA* for Patients with Type 2 Diabetes

NARRATIVE	ON-SCREEN TEXT/GRAPHICS	DIRECTIONS
Click here to start the Progress check.	**Progress Check** Robot: Congratulations! You've made it through the last section! I could use one more refueling before we continue on. Hopefully you can help me refuel my battery by correctly answering the following questions. **Click here to start the progress check**	

IM05100

Using *AVANDIA* for Patients with Type 2 Diabetes

NARRATIVE	ON-SCREEN TEXT/GRAPHICS	DIRECTIONS
None	**Progress Check** 1. In the fixed dose pivotal study 095, what was the reduction in HbA_{1c} with *AVANDIA* 4 mg plus insulin compared to insulin alone? **A. –0.6%** B. –0.9% C. –1.0% D. –1.2%	

Incorrect Answer Feedback

In study 095, *AVANDIA* 4 mg in combination with insulin resulted in a 0.6% reduction in HbA_{1c} compared to insulin alone.

IM05110
Using *AVANDIA* for Patients with Type 2 Diabetes

NARRATIVE	ON-SCREEN TEXT/GRAPHICS	DIRECTIONS
None	**Progress Check** 2. In the fixed dose pivotal study 082, what was the reduction in FPG with *AVANDIA* 4 mg plus insulin compared to insulin alone? A. 10% B. **40%** C. 80% **D.** 90%	

Incorrect Answer Feedback
In study 082, *AVANDIA* 4 mg in combination with insulin resulted in a 40% reduction in HbA_{1c} compared to insulin alone.

IM05120
Using *AVANDIA* for Patients with Type 2 Diabetes

NARRATIVE	ON-SCREEN TEXT/GRAPHICS	DIRECTIONS
None	**Progress Check** 3. When prescribing *AVANDIA* in combination with insulin for patients with type 2 diabetes, what action should be taken if hypoglycemia occurs? A. Reduce the *AVANDIA* dose **B. Reduce the insulin dose by 10–25%** C. Reduce both *AVANDIA* and insulin doses D. None of the above	

Incorrect Answer Feedback
According to the *AVANDIA* PI, if hypoglycemia occurs, the insulin dose should be reduced by 10–25%.

IM05130
Using *AVANDIA* for Patients with Type 2 Diabetes

NARRATIVE	ON-SCREEN TEXT/GRAPHICS	DIRECTIONS
None	**Progress Check** 4. Approximately what percentage of all patients treated with *AVANDIA* were able to reduce their insulin dose? A. 10% **B. 40%** C. 60% D. None of the above	

Incorrect Answer Feedback
According to the *AVANDIA* PI, 40% of patients in the clinical studies were able to reduce their insulin dose.

IM05140
Using *AVANDIA* for Patients with Type 2 Diabetes

NARRATIVE	ON-SCREEN TEXT/GRAPHICS	DIRECTIONS
Click the <Return> button to go back to the Main Menu.	**Progress Check** Robot: Great job! You've replenished my energy! Click the <Return> button to return to the main menu.	

IM06010
Printable Summary

NARRATIVE	ON-SCREEN TEXT/GRAPHICS	DIRECTIONS
Click the <Open Summary> button to view or print this module.	**Printable Summary** The Program Summary is provided in Adobe Acrobat format. Simply click on the button below to open the file. The file will appear in a pop-up window and may take up to several minutes to open. Please be patient! **<Open Summary>** **Robot: Here's a summary of this module. You can view or print this document.**	

Use of *AVANDIA* in Combination with Insulin for the Treatment of Type 2 Diabetes

Diabetes Mellitus - Overview

Core Defects of Type 2 Diabetes

Type 1 Diabetes
- Up to 10% of all diabetes cases
- Typically occurs during childhood or adolescence
- Absolute endogenous insulin deficiency due to acute beta-cell failure (autoimmune)
- Exogenous insulin therapy is required to control blood glucose levels

Type 2 Diabetes
- Approximately 90% of all diabetes cases
- Typically occurs in adulthood, but increasingly in childhood and adolescence
- Commonly associated with obesity
- A complex disease process of increased insulin resistance at the target level eventually leading to progressive beta-cell failure

Historically, as insulin resistance worsens, greater demand is placed on the beta-cells, requiring patients to become dependent on insulin therapy

Complications of Diabetes

Uncontrolled diabetes can lead to serious and potentially life-threatening complications:

Microvascular
- ***Retinopathy***
- ***Neuropathy***
- ***Nephropathy***

Macrovascular
- ***Cardiovascular disease***
- ***Cerebrovascular disease***

Important to Know:

- According to the United Kingdom prospective Diabetes Study (UKPDS), every 1% increase above goal elevates the risk of diabetic complications, including:
  - 21% increase in any diabetes-related endpoint
  - 14% increase in risk of myocardial infarction (MI)
  - 12% increase in risk of stroke
  - 37% increase in risk of microvascular complications

Medical expenses for people with diabetes are 5 times that of people without diabetes

Understanding Type 2 Diabetes

- Type 2 diabetes is a progressive and incurable disease
- Patients slowly become unable to produce or use insulin to control glucose levels as the body becomes more insulin resistant
- Treatment of type 2 diabetes is often advanced with progression of the disease along the following continuum:
  - Diet and exercise
  - Oral anti-diabetic drugs (OADs)
  - Increase OAD dose
  - Combination OAD
  - OAD combination with insulin
  - Insulin
- *AVANDIA* indications:
  - Adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes mellitus
  - Use as monotherapy, and in combination with a sulfonylurea, metformin, or insulin when diet, exercise, and a single agent do not result in adequate glycemic control
- *AVANDIA* strategy:
  - Recently diagnosed patients with type 2 diabetes who are not at goal (HbA_{1c} <7%) with diet and exercise
  - Patients with type 2 diabetes who are not at goal (HbA_{1c} <7%) with a sulfonylurea
  - Patients with type 2 diabetes who are on insulin
- *AVANDAMET* indications:
  - Adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes who are already treated with combination rosiglitazone and metformin or who are not adequately controlled on metformin alone
- *AVANDAMET* strategy:
  - Patients with type 2 diabetes who are not at goal (HbA_{1c} <7%) with metformin

Important to Know:

- Among adults with diagnosed diabetes, about 11% take both insulin and oral medications, 22% take insulin only, 49% take oral medications only, and 17% do not take either insulin or oral medications. (National Diabetes Fact Sheet, 2002)

Physicians often administer Insulin (for a short period of time) to manage acute episodes of elevated blood glucose levels (>250 mg/dl). Patients are usually titrated off insulin once glucose levels drop down to a range where they can be managed by oral therapy.

Role of Insulin in Glucose Control

Insulin enables the body to maintain proper glucose balance.

- Reduces hepatic glucose output
- Stimulates glucose uptake in tissues
- Inhibits lipolysis (breakdown of triglycerides into glycerol and free fatty acids)

Important to Know:

Glucose levels in the blood stream help regulate the amount of insulin secreted by the beta-cells in the pancreas.

Insulin Resistance

Normal Physiology

- Insulin binds to receptors on the cell surfaces to facilitate glucose transport

Insulin Resistance

- Impaired physiologic action of insulin receptors and possible decrease in the number of insulin receptors (**down regulation**) leads to the accumulation of insulin and increased circulating glucose
- Insulin resistance is believed to precede beta-cell impairment in type 2 diabetes

Competitive Connection:

- Impairment of insulin secretion and/or insulin sensitivity may result in hyperglycemia
- In the management of diabetes, it is critical to target core defects of type 2 diabetes: Insulin resistance and beta-cell impairment

Beta-cell Impairment

- As insulin resistance worsens, beta-cells produce more insulin
- The beta-cells become overworked
- The beta-cells' ability to produce insulin declines over time
- The decline in beta-cell function leads to initiation of insulin therapy

Competitive Connection:
- *AVANDIA* may delay the progression of type 2 diabetes by targeting insulin resistance and improving estimates of beta-cell function
- In long-term extension studies, *AVANDIA* is the only TZD with durability as monotherapy for up to 3½ years*

*Patients who received AVANDIA 8 mg QD and 4 mg BID for at least 42 months during 2 double-blind, 26-week, placebo-controlled trials and their open-label extensions. Results of these trials are biased because they include only those patients who elected to continue on AVANDIA therapy for the full duration. Patients demonstrated sustained efficacy over time in these "completers."

*Diabetes Treatment **Matrix***

Traditional Treatment Matrix
- TZDs reserved for third-line therapy
- After secretagogue and metformin failure
- Late in the treatment continuum

Important to Know:
- 62% of patients on OADs are not at the ADA goal of HbA_{1c} <7%
-)

Alternative Treatment Matrix
- Early use of TZDs as monotherapy or in combination with other OADs
- Target insulin resistance and beta-cell impairment
- Help slow disease progression and the need for insulin

OAD Treatment Rationale
- Insulin sensitizers target core defects of insulin resistance and declining beta-cell function
- Secretagogues stimulate beta-cell function at the pancreas

- Insulin compensates for late-stage beta-cell failure

Competitive Connection:
- At 26 weeks, compared to placebo, *AVANDIA* 8 mg/day monotherapy targets core defects of type 2 diabetes:
  - Reducing insulin resistance by 35.5%

Improving estimates of beta-cell function by 65.7%

AVANDIA Use with Insulin

Prevalence of Insulin Use
- 8.0 million patients take insulin plus an OAD
- 1.0 million patients take insulin alone (GSK assumption)
- 1.5 million patients take insulin with a TZD
  - 10.5% of *AVANDIA*'s prescriptions are in combination with insulin (approximately 768,206 patients)
  - 14.2% of Actos' prescriptions are in combination with insulin (approximately 776,121 patients)

Competitive Connection:
- Until now, Actos was the only TZD approved for use with insulin
- *AVANDIA* 4mg/day is now approved for use in combination with insulin

Types of Insulin

Insulin therapies are categorized according to their duration of activity in the body:

Click on each insulin type to view products.

Insulin Type	Onset	Peak	Duration
Rapid-Acting	10-15 minutes	30-90 minutes	3-5 hours
Short-Acting	30-60 minutes	50-120 minutes	5-8 hours
Intermediate-Acting	1-3 hours	7-15 hours	18-24 hours
Long-Acting	1-8 hours	8-12 hours	24-36 hours
Mixed Insulins	The onset, peak, and duration of action of these mixtures would reflect a composite of the intermediate and short- or rapid-acting components, with one peak of action		

DID YOU KNOW…

Lantus (glargine)—is the first FDA-approved (April 2000) recombinant human insulin analog, which works quickly (onset of action: 1 hour) to provide consistent, 24-hour coverage similar to that provided by the normal pancreas, *without* the pronounced peak in serum levels observed with human insulin. (Lantus.com)

Rapid-acting insulin

- Humalog® (*Lilly*)
- Iletin® II (*Lilly*)
- Novolog® (*Novo Nordisk*)

Short-acting insulin

- Humulin® R(*Lilly*)
- Novolin® (*Novo Nordisk*)

- Velosulin® (*Novo Nordisk*)

Intermediate-acting insulin
- Humulin® N (*Lilly*)
- Humulin® L (*Lilly*)
- Lente® Iletin® II (*Lilly*)
- Novolin® N (*Novo Nordisk*)
- Novolin® L (*Novo Nordisk*)

Mixed insulins
- Humulin® 50/50 (*Lilly*)
- Humulin® 70/30 (*Lilly*)
- Humalog® Mix 75/25™ (*Lilly*)
- Humalog® 50/50 (*Lilly*)
- Novolin® 70/30 (*Novo Nordisk*)
- Novolog® Mix 70/30 (*Novo Nordisk*)

Long-acting insulin
- Humulin® U (*Lilly*)
- Lantus® (glargine) (Aventis) (Physician's Desk Reference) (FDA Consumer Magazine)

Advantages of insulin therapy
- Immediate onset of action
- Experience—physicians are generally comfortable using insulin

Disadvantages of insulin therapy
- Potential hypoglycemia
- Potential subcutaneous tissue infection (reactions include redness, pain, itching, hives, swelling, and inflammation)
- Careful glucose monitoring and dose adjustments may be necessary in patients with renal or hepatic dysfunction
- No effect on insulin resistance
- Must be refrigerated

Using AVANDIA for Patients with Type 2 Diabetes

When to Choose *AVANDIA*

1. Early in the course of disease (recently diagnosed type 2 diabetes) to target insulin resistance and improve estimates of beta-cell function:
    - ***AVANDIA monotherapy***
2. When patients are not at goal (HbA_{1c} <7%) with sulfonylurea monotherapy:
    - ***AVANDIA combination therapy***
3. Late in the course of disease when patients are on insulin:
    - ***AVANDIA with insulin***

When to Choose *AVANDAMET*

3. When patients are not at goal (HbA_{1c} <7%) with metformin monotherapy
4. When patients are at goal (HbA_{1c} <7%) with metformin and *AVANDIA* and can benefit from the convenience of a fixed-dose combination

(NOTE: *AVANDAMET* is not indicated for use in combination with insulin)

Competitive Connection:

- *AVANDIA* is the only TZD providing proven durability as monotherapy for up to 3½ years*
- *AVANDIA* and metformin in combination provides sustained additive and durable glycemic control for up to 2½ years†

*Patients who received AVANDIA 8 mg QD and 4 mg BID for at least 42 months during 2 double-blind, 26-week, placebo-controlled trials and their open-label extensions. Results of these trials are biased because they include only those patients who elected to continue on AVANDIA therapy for the full duration. Patients demonstrated sustained efficacy over time in these "completers."

† Patients who received rosiglitazone 4 mg BID plus metformin 2.5 g/day for at least 30 months during a double-blind, randomized study (6 months duration) and/or its open-label extension. Results of this trial are biased because they include only those patients who elected to continue on rosiglitazone plus metformin for the full duration. Patients demonstrated sustained efficacy over time in these "completers."

DID YOU KNOW…

Traditional monotherapy does not treat the core defects associated with type 2 diabetes. At the time of diagnosis, beta-cell function has already started to decline significantly. Regardless of treatment with sulfonylurea or metformin, beta-cell function continues to decline as time goes on.

In the alternative treatment matrix, early use of ***AVANDIA*** **provides clear benefits:** Reduce insulin resistance and improve estimates of beta-cell function.

AVANDIA **Monotherapy** – ***AVANDIA*** 4 mg bid provides durability through insulin sensitization, reducing insulin resistance by up to 35.5% and improving estimates of beta-cell function by up to 65.7% compared to placebo at 26 weeks. In long-term extension studies, *AVANDIA* is the only TZD providing documented durability as monotherapy for up to 3½ years.*

AVANDIA **Combination Therapy** – *AVANDIA* 2mg bid provided enhanced glycemic control in combination with sulfonylureas at Week 26:

- 1.4 % reduction in HbA_{1c}
- Low incidence of hypoglycemia (4.8%) in combination with sulfonylureas (Date on file)

AVANDIA **with Insulin –** *AVANDIA* significantly reduces FPG and HbA_{1c} in patients who are not at goal (HbA_{1c} <7%) on insulin. (*AVANDIA* PI)

- Approximately 40% of all patients treated with *AVANDIA* reduced their insulin dose (*AVANDIA* PI)

AVANDIA **and metformin in combination**—provides sustained glycemic control for up to 2.5 years, providing additive glycemic control of FPG and HbA_{1c} compared to metformin monotherapy.† (*AVANDAMET* Overcoming Barriers)

*Patients who received AVANDIA 8 mg QD and 4 mg BID for at least 42 months during 2 double-blind, 26-week, placebo-controlled trials and their open-label extensions. Results of these trials are biased because they include only those patients who elected to continue on AVANDIA therapy for the full duration. Patients demonstrated sustained efficacy over time in these "completers."

† Patients who received rosiglitazone 4 mg BID plus metformin 2.5 g/day for at least 30 months during a double-blind, randomized study (6 months duration) and/or its open-label extension. Results of this trial are biased because they include only those patients who elected to continue on rosiglitazone plus metformin for the full duration. Patients demonstrated sustained efficacy over time in these "completers."

AVANDIA **indications:**

- Adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes mellitus
- Use as monotherapy, and in combination with a sulfonylurea, metformin, or insulin when diet, exercise, and a single agent do not result in adequate glycemic control

NOTE: In the *AVANDIA* PI, safety data are provided for both the 4 mg/day and 8 mg/day doses, although only *AVANDIA* 4 mg/day is approved for use in combination with insulin.

Overview of Efficacy and Safety Studies

The efficacy and safety of *AVANDIA* in combination with insulin have been evaluated in a number of studies that included:

- Two fixed-dose pivotal studies (studies 082 & 095)
- One 26-week study included patients with renal failure (Study 136)
- One 26-week study included patients who were well-controlled on insulin (Study 085)

Important to Know:
In the above studies, patients used various insulin formulations including regular, isophane, zinc suspension products, and Humalog® (insulin lispro [rDNA origin] injection, Eli Lilly and Company)**.** Studies have not been conducted to evaluate the use of *AVANDIA* and Lantus® (insulin glargine [rDNA origin] injection, Aventis Pharmaceuticals)

Fixed Dose, Pivotal Trials (study 082 and study 095)

Study Objectives

Evaluate the efficacy and safety of *AVANDIA* in combination with insulin

Study Design

- Two randomized, 26-week, fixed dose, double-blind, placebo-controlled trials
- Patients had to meet the following inclusion criteria:
    - Diagnosis of type 2 diabetes mellitus
    - Fasting C-peptide ≥ 0.4 ng/ml
    - $HbA_{1c} \geq 7.5\%$
    - Receiving ≥ 30 units of insulin daily at screening
    - FPG between 140 and 300 mg/dl during a 4-week placebo run-in period
- Patient were excluded if they met any of the following criteria:
    - Clinically significant renal disease
    - Hepatic disease

    - Significant anemia
    - Severe angina, coronary insufficiency, or heart failure
- Patients were randomized to receive *AVANDIA* 4 mg total daily dose, *AVANDIA* 8 mg total daily dose, or placebo in addition to the insulin injections.
- Insulin dose reductions were permitted only in response to sustained hypoglycemia

Efficacy Parameters

- The primary efficacy parameters in both studies were the mean change from baseline and placebo in HbA_{1c} at the end of 26 weeks of therapy.
- Secondary parameters included:
    - FPG,
    - Total daily insulin dose
    - Percent change in daily insulin dose

Safety

- Most reported adverse events were mild-to-moderate in intensity and unrelated to *AVANDIA*
- Adverse events occurring in >10% of patients included:
    - Hypoglycemia
    - Upper respiratory tract infection
    - Anemia
- The median weight gain in patients on insulin alone was 0.9 kg compared to 4.1 kg in patients who received *AVANDIA* 4 mg/day plus insulin
    - 6.8% of patients receiving *AVANDIA* in combination with insulin withdrew from the studies due to an adverse event

Safety in Two Clinical Studies

- Hypoglycemia was the most frequently reported adverse event, but resulted in <1% of withdrawals (4/408)
- Cardiac failure was reported in 1.9% of patients receiving *AVANDIA* bid plus insulin compared to 3.1% of patients receiving *AVANDIA* QD plus insulin, and 1% of patients receiving insulin alone

Important to Know:
The double-blind studies included patients with long-standing diabetes (mean, 12 years) and a high prevalence of pre-existing medical conditions including:

- Peripheral neuropathy
- Retinopathy
- Ischemic heart disease
- Vascular disease
- Congestive heart failure

The frequency of these concomitant illnesses was approximately twice that of the pre-marketing double-blind studies with *AVANDIA* as monotherapy and in combination with metformin or a sulfonylurea.

This may help to explain the increased incidence of edema, cardiac failure, and cardiovascular adverse events observed in patients receiving *AVANDIA* and insulin combination therapy compared to insulin alone. It was not possible to determine specific risk factors that could be used to identify all patients at risk for heart failure and other cardiovascular events on combination therapy.

***AVANDIA* Dosing in Combination with Insulin**

For patients stabilized on insulin, the insulin dose should be continued upon initiation of *AVANDIA*. *AVANDIA* should be dosed at 4 mg daily. Doses of *AVANDIA* greater than 4 mg daily in combination with insulin are not currently indicated. It is recommended that the insulin dose be decreased by 10% to 25% if the patient reports hypoglycemia or if FPG concentrations decrease to less than 100 mg/dl. (*AVANDIA* PI)

IM07010
Final Assessment

NARRATIVE	ON-SCREEN TEXT/GRAPHICS	DIRECTIONS
None	**Final Assessment Introduction** You are about to take the Final Assessment. The Final Assessment consists of about 10 questions in multiple choice or true & false formats. Once you begin the final assessment, you cannot re-take the assessment after submitting your score to e-FORCE. You must achieve a score of 80% for this course to be considered complete. We highly recommend that you review the Program Summary before proceeding in order to make sure that you have covered all key points. You may access the Program Summary from the Main Menu. **<Sorry, Not Ready Yet>** **<Let's Go, I Am Ready>** Robot: Are you ready or what?	

IM07020
Final Assessment

NARRATIVE	ON-SCREEN TEXT/GRAPHICS	DIRECTIONS
None	1. Insulin therapy is required because of which of the following physiologic defects? A. Increased release of hepatic glucose B. Decreased levels of circulating glucose C. Increased resistance to the effects of insulin by tissues **D. Decreased beta-cell function (failure)**	

IM07030
Final Assessment

NARRATIVE	ON-SCREEN TEXT/GRAPHICS	DIRECTIONS
None	2. What therapeutic benefit does *AVANDIA* provide in patients with type 2 diabetes who are not at goal (HbA_{1c} less than 7%) on insulin? A. Significant reduction in FPG B. Significant reduction in HbA_{1c} **C. Significant reduction in FPG and HbA_{1c}** D. None of the above	

IM07040
Final Assessment

NARRATIVE	ON-SCREEN TEXT/GRAPHICS	DIRECTIONS
None	3. By which process does insulin enable the body to maintain proper glucose balance? A. Reduces hepatic glucose output B. Stimulates glucose uptake in tissues C. Inhibits lipolysis **D. All of the above**	

IM07050
Final Assessment

NARRATIVE	ON-SCREEN TEXT/GRAPHICS	DIRECTIONS
None	4. According to an alternative treatment matrix, when is it appropriate to prescribe a secretagogue? A. Early in the course of disease to combat insulin resistance **B. Third-line, to stimulate pancreatic beta-cells** C. At any time in the treatment continuum	

IM07060
Final Assessment

NARRATIVE	ON-SCREEN TEXT/GRAPHICS	DIRECTIONS
None	5. What HbA_{1c} level was required for inclusion into the fixed-dose pivotal studies with *AVANDIA* in combination with insulin? A. Greater than or equal to 6.0% B. Greater than or equal to 7.0% **C. Greater than or equal to 7.5%** D. Greater than or equal to 8.0%	

IM07070
Final Assessment

NARRATIVE	ON-SCREEN TEXT/GRAPHICS	DIRECTIONS
None	6. Which of the following is not a serious and potentially life-threatening complication of uncontrolled diabetes? A. Nephropathy **B. Hypotension** C. Cardiovascular disease D. Peripheral vascular disease	

IM07080
Final Assessment

NARRATIVE	ON-SCREEN TEXT/GRAPHICS	DIRECTIONS
None	7. With the FDA approved indication for the use of *AVANDIA* in combination with insulin, when is it appropriate to prescribe *AVANDIA* for patients with type 2 diabetes? A. Early in the course of disease (recently diagnosed type 2 diabetes) as monotherapy to target insulin resistance and improve estimates of beta-cell function B. When patients are not at goal (HbA_{1c} less than 7%) with sulfonylurea therapy C. Late in the course of disease in patients who are not at goal (HbA_{1c} less than 7%) on insulin **D. All of the above**	

IM07090
Final Assessment

NARRATIVE	ON-SCREEN TEXT/GRAPHICS	DIRECTIONS
None	8. When is it appropriate to prescribe *AVANDAMET* for patients with type 2 diabetes? A. When patients are not at goal (HbA_{1c} less than 7%) with metformin monotherapy B. When patients are at goal (HbA_{1c} less than 7%) on metformin and Avandia and can benefit from the convenience of a fixed-dose combination C. When patients are not at goal (HbA_{1c} less than 7%) on insulin **D. A and B**	

IM07100
Final Assessment

NARRATIVE	ON-SCREEN TEXT/GRAPHICS	DIRECTIONS
None	9. With which types of insulin may *AVANDIA* be used in combination? A. Short- and Rapid-acting insulins B. Intermediate-acting insulin **C. All types of insulin** D. Long-acting insulin	

IM07110

Final Assessment

NARRATIVE	ON-SCREEN TEXT/GRAPHICS	DIRECTIONS
None	10. In study 095, what was the reduction in FPG achieved with *AVANDIA* 4 mg plus insulin compared to insulin alone? A. 42% **B. 32%** C. 23% D. 16%	

IM07120

Final Assessment

NARRATIVE	ON-SCREEN TEXT/GRAPHICS	DIRECTIONS
None	**Final Assessment Complete** You have completed the Final Assessment. You may go back and change your answers before clicking the "Complete" button below. Please note, once you click "Complete", you will be unable to change your answers and will be taken to the score page. **<Complete>**	

IM07120

Final Assessment

NARRATIVE	ON-SCREEN TEXT/GRAPHICS	DIRECTIONS
None	**Final Assessment Complete** **If passing score:** Congratulations! You have passed! Your score is __% Click <Submit> to submit your scores to e-FORCE. **If failing score:** You have not passed this program. Your score is ___% Please click the <Submit> button to submit your scores to e-FORCE.	

IM07130

Final Assessment

NARRATIVE	ON-SCREEN TEXT/GRAPHICS	DIRECTIONS
None	**Final Assessment in Progress** You have already partially completed the Final Assessment. Please click the <Continue> button below to continue where you left off.	

IM07140

Final Assessment

NARRATIVE	ON-SCREEN TEXT/GRAPHICS	DIRECTIONS
None	**Final Assessment Complete** You have already submitted your score. Please click the <Return> button below to return to the main menu.	

IM08010
Exit Screen

NARRATIVE	ON-SCREEN TEXT/GRAPHICS	DIRECTIONS
None	Are you sure you want to exit? [If no] Return user to main menu [If yes] exit program to LMS	Pop-up box Display Tricore Logo and GSK Logo