

INTRODUCING
ISENTRESS 600 mg
FOR ONCE-DAILY DOSING

at 1200 mg (2 x 600 mg)

**Sales Manager
Coaching Guide**


Isentress[™] 600_{mg}
raltegravir, MSD

NOTE TO COUNTRIES: Use of this discussion guide requires local medical legal review for use, and must conform with all applicable SOPs, laws, and regulations.

EFFICACY

TOLERABILITY

ONCE DAILY



Plan



Your precall plan should include:

- Call objective
- How you will open the call
- Open-ended, thought-provoking questions to ask to uncover belief(s) that will help you meet your call objective
- Close or call to action to execute on your objective

Open



Use the front cover to open your discussion of ISENTRESS 600 mg.

VERBALIZATION

Insight:

Treating HIV is a marathon, not a sprint. The bicyclist image shown on the front cover conveys the strength and endurance of ISENTRESS to help HIV patients on their journey.

COACHING GUIDE



Open the Interaction

Doctor, we have discussed how your HIV patients have benefited from a regimen that included ISENTRESS due to its efficacy and tolerability. And I'm sure you would agree that after more than 10 years on the market, ISENTRESS is still going strong.

Well, I have some exciting news to share with you—ISENTRESS 600 mg is now available with the added convenience of once-daily dosing.

Coaching Tips



Ask the representative about their PRECALL PLAN for a target customer in their territory:

- Based on your precall plan, what do you think this physician's response will be to the new QD dosing for ISENTRESS?
- What types of patients have you discussed with this physician in the past?
- To what specific data do you think this physician will respond?
- Is the representative prepared to identify the opportunity with open-ended, thought-provoking questions?

Listen for the following as the representative OPENS the call:

- Interest-generating Open that focuses on the long-term experience of ISENTRESS and the confidence that physicians can have in prescribing ISENTRESS for their HIV patients.
- Enthusiastic delivery of first key message—ISENTRESS 600 mg is now available with the added convenience of once-daily dosing.

TWICE DAILY

ISENTRESS™ raltegravir, MSD **10+ years of proven experience**

WORLD'S FIRST INTEGRASE INHIBITOR

- With over 1.1 million estimated patient treatment years^{1,2}

THE ONLY INTEGRASE INHIBITOR

- With 5 years of long-term efficacy data in clinical trials³⁻⁴
- Metabolized mainly by the UGT1A1 pathway without CYP450 contribution^{2,4}
- Indicated for patients from 4 weeks of age through adulthood^{1,4,5}

PROVEN EFFICACY IN TREATMENT-NAÏVE ADULTS
Superior vs an NNRTI⁶ | Non-inferior vs select PIs⁴ | Non-inferior vs another INSTI⁴

DEMONSTRATED TOLERABILITY⁸

Recommended INSTI-based regimen for treatment-naïve patients since 2009⁹

¹Estimates for patient treatment years were calculated for ISENTRESS 400-mg film-coated tablets based on the assumption that each patient takes the recommended dose of one 400-mg tablet twice daily. Patient treatment years of exposure to ISENTRESS was estimated from sell data provided by the IMS Health MIDAS market research database during a period from 27 September 2007 through 26 March 2017.

²ISENTRESS 600 mg is not indicated in pediatric patients under 40 kilograms.

INSTI = integrase strand transfer inhibitor; NNRTI = non-nucleoside reverse transcriptase inhibitor; PI = protease inhibitor; diphosphate, diphosphate, diphosphate.

Insert appropriate Indications and local Selected Safety Information (SSI) for ISENTRESS (ISENTRESS 400 mg), as applicable, here. The current global SSI can be found here: editorial.merck.com

ONCE DAILY

Now with the added convenience of **once-daily dosing** at 1200 mg (2 x 600 mg)

The 400-mg tablet should not be used to administer 1200-mg once-daily regimen

GOING STRONG

Isentress™ 600mg
raltegravir, MSD

Insert appropriate Indications and local Selected Safety Information (SSI) for ISENTRESS and/or ISENTRESS 600 mg, as applicable, here. The current global SSI can be found here: editorial.merck.com

Insight:

Market research revealed that physicians want to be reminded of all the reasons they use ISENTRESS today.

Identify & Confirm

Ask open-ended, thought-provoking questions about the physician's perceptions of ISENTRESS to date.

VERBALIZATION

Share Information

Use the left page of the first spread to set the stage by reminding the customer of the heritage of ISENTRESS.

VERBALIZATION

COACHING GUIDE

Identify and Confirm



Doctor, what has your clinical experience been with ISENTRESS?

Doctor please share with me, what patient types do you treat with ISENTRESS?

Share Information



...I am glad to hear that you have had such great clinical experience with ISENTRESS and your patients have benefited. You know, ISENTRESS has more than 10 years of proven clinical experience and was the world's first integrase inhibitor. Even today, ISENTRESS is still the only integrase inhibitor with long-term efficacy of 5 years demonstrated in clinical trials. That's proven long-term efficacy that your HIV patients can count on.

ISENTRESS is the only integrase inhibitor metabolized mainly by the UGT1A1 pathway without CYP450 contribution. That means fewer clinically significant drug interactions, unanticipated adverse reactions, and therapeutic failures in your patients. And it is the only integrase inhibitor indicated for your pediatric patients from 4 weeks of age through adulthood.

Doctor, ISENTRESS has proven efficacy in treatment-naïve adults; has been proven superior versus an NNRTI; proven non-inferior vs select PIs; and proven non-inferior vs another INSTI. ISENTRESS also has demonstrated tolerability, and has been a recommended INSTI-based regimen for treatment-naïve patients since 2009. All excellent reasons why you have chosen ISENTRESS time and time again.

Coaching Tips



Listen for the following as the representative asks questions to IDENTIFY or CONFIRM the customer's needs:

- Focused questions designed to identify or confirm the physician's perceptions of ISENTRESS 400 mg to date
 - Open-ended, thought-provoking questions, if the purpose is to identify needs
 - Closed questions, if the purpose is to confirm needs

Listen for the following as the representative SHARES key messages:

- Descriptive summary enumerating the major attributes of ISENTRESS 400 mg BID.

TWICE DAILY

ISENTRESS™
raltegravir, MSD | 10+ years of proven experience

WORLD'S FIRST
INTEGRASE INHIBITOR

- With over 1.1 million estimated patient treatment years^{1,2}

THE ONLY
INTEGRASE INHIBITOR

- With 5 years of long-term efficacy data in clinical trials³⁻⁴
- Metabolized mainly by the UGT1A1 pathway without CYP450 contribution^{5,6}
- Indicated for patients from 4 weeks of age through adulthood^{2,4,5}

PROVEN EFFICACY IN TREATMENT-NAÏVE ADULTS
Superior vs an NNRTI⁷ | Non-inferior vs select PI⁸ | Non-inferior vs another INSTI⁹

DEMONSTRATED TOLERABILITY⁹

Recommended INSTI-based regimen for treatment-naïve patients since 2009⁹

*Estimates for patient treatment years were calculated for ISENTRESS 400-mg film-coated tablets based on the assumption that each patient takes the recommended dose of one 400-mg tablet twice daily. Patient treatment years of exposure to ISENTRESS was estimated from and were provided by the IMS Health MIDAS market research database during a period from 27 September 2007 through 26 March 2017.
¹ISENTRESS 600 mg is not indicated in pediatric patients under 40 kilograms.
 INSTI = integrase strand transfer inhibitor, NNRTI = non-nucleoside reverse transcriptase inhibitor, PI = protease inhibitor, UGT = uridine diphosphate glucuronosyltransferase.

Insert appropriate Indications and local Selected Safety Information (SSI) for ISENTRESS (oral ISENTRESS 400 mg), as applicable, here.
 For current global SSI, visit www.editorial.merck.com

ONCE DAILY

Now with the added convenience of **once-daily dosing** at 1200 mg (2 x 600 mg)

The 400-mg tablet should not be used to administer 1200-mg once-daily regimen

GOING STRONG

Isentress™ 600mg
raltegravir, MSD

Insert appropriate Indications and local Selected Safety Information (SSI) for ISENTRESS and/or ISENTRESS 600 mg, as applicable, here.
 The current global SSI can be found here: www.editorial.merck.com

Insight:

Note the "TWICE DAILY" and "ONCE DAILY" banners across the top of the spread that cue you to the formulation under discussion. It's important to attribute the data to the correct formulation as clinical trials for ISENTRESS 600 mg used ISENTRESS as a comparator.

Identify & Confirm

Ask open-ended, thought-provoking questions about the physician's thoughts on once-daily dosing.

VERBALIZATION

Share Information

Now that you've set the stage, use the right side of the spread to introduce ISENTRESS 600 mg with the added convenience of once-daily dosing.

VERBALIZATION

COACHING GUIDE

Identify and Confirm



Doctor, share with me, what are some of the challenges you face with managing your HIV patients complex treatment regimens?

Now that ISENTRESS 600 mg is available in once-daily dosing, how does that change how you manage and treat your HIV patients?

Share Information



Doctor, you chose ISENTRESS for your HIV patients for all the reasons we've discussed and now you have one more—the added convenience of once-daily dosing with ISENTRESS 600 mg.

Coaching Tips



Listen for the following as the representative asks questions to IDENTIFY or CONFIRM the customer's needs:

- Focused, concise question(s) designed to identify or confirm the physician's thoughts on once-daily dosing
 - Was the representative able to uncover the challenges the physician faces managing the complex treatment regimens of his/her HIV patients?

Listen for the following as the representative SHARES key messages:

- Strong statement linking the physician's experience with ISENTRESS 400 mg to the added convenience of once-daily dosing with ISENTRESS 600 mg.

ONCE DAILY
ONCEMRK
4.8-WEEK DATA

raltegravir, MSD
 For once-daily dosing at 1200 mg (2 x 600 mg)

Proven efficacy comparable with ISENTRESS¹

Robust viral suppression¹

Percentage of patients with HIV-1 RNA <40 copies/mL at 48 weeks (NC=F approach)²

88.9%
88.3%

NC=F: Non-completers were considered failures.
ISENTRISS 600 mg + ISENTRESS 195% CI=0.5 (-4.2, 5.2)

ONCEMRK STUDY DESIGN

Randomized, double-blind, active-controlled superiority study in treatment-naïve HIV-1-infected patients ≥18 years of age with HIV-1 RNA >1,000 copies/mL to evaluate the safety and antiretroviral activity of ISENTRESS 600 mg (q.d. 1200 mg [2 x 600 mg] once daily) + TDF/FTC (n=531) vs ISENTRESS 1800 mg twice daily + TDF/FTC (n=266). The primary end point was noninferiority with respect to the percentage of patients with HIV-1 RNA <40 copies/mL at Week 48. A secondary end point was change from baseline in CD4 cell count at Week 48.

Insert appropriate Indications and local Selected Safety Information (SSI) for ISENTRESS[®] and/or ISENTRESS 600 mg, as applicable, here.
The current global SSI can be found here: editorial.merck.com.

Effective viral suppression regardless of baseline viral load

>100,000 HIV-1 RNA copies/mL at baseline

86.7%	83.8%
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≤100,000 HIV-1 RNA copies/mL at baseline

97.2%	97.7%
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CI = observed failure (baseline values carried forward for patients who discontinued due to lack of efficacy)

Similar increases in CD4 count

Mean change from baseline in CD4 cell count at 48 weeks (OF approach)

ISENTRESS 600 mg + TDF/FTC (n=532) +232	ISENTRESS + TDF/FTC (n=266) +234	Baseline CD4 cell count was <350 cells/mm ³ for ISENTRESS + TDF/FTC. CI = observed failure (baseline values carried forward for patients who discontinued due to lack of efficacy). ISENTRESS 600 mg + ISENTRESS 195% CI=0.2 (-0.1, 4.2) ¹
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Virologic and immunologic efficacy were similar to ISENTRESS irrespective of:

- Hepatitis B coinfection status
- Gender
- Hepatitis C coinfection status
- Race/ethnicity
- Baseline CD4 cell count
- Geographic region

CD4 = cluster of differentiation 4; CI = confidence interval; FTG = zalcitabine; HIV-1 = human immunodeficiency virus type 1; RNA = ribonucleic acid; TDF = tenofovir disoproxil fumarate.

Insight:

The primary end point in ONCEMRK was noninferiority with respect to the percentage of patients with HIV-1 RNA <40 copies/mL at Week 48. It is more common to assess efficacy of an HIV therapy based on attainment of <50 copies/mL.

Identify & Confirm

Ask open-ended, thought-provoking questions about the physician's thoughts on viral suppression.

VERBALIZATION

Share Information

Use the left page of the second spread to introduce the ONCEMRK efficacy data that supports once-daily dosing.

VERBALIZATION

COACHING GUIDE

For once-daily dosing at 1200 mg (2 x 600 mg)

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Identify and Confirm



*Doctor, what do you expect from an HIV therapy in regard to viral suppression?
Does the viral suppression provided by ISENTRESS 400 mg meet your expectations?*

*Doctor, you have been prescribing ISENTRESS 400 mg BID for some time now.
What is your perception of the viral suppression provided by ISENTRESS?*

*Doctor, could you share an example of one of your HIV patients' response to
ISENTRESS 400 mg BID in terms of viral suppression? Have you been satisfied with
the results achieved?*

Share Information



Doctor, ISENTRESS 600 mg has proven efficacy comparable with ISENTRESS. In a randomized, double-blind, active-controlled noninferiority study in 797 treatment-naïve HIV-infected patients ≥ 18 years of age with HIV-1 RNA $\geq 1,000$ copies/mL, 88.9% of patients in the ISENTRESS 600 mg group achieved HIV-1 RNA < 40 copies/mL at 48 weeks, and 88.3% of patients in the ISENTRESS group achieved HIV-1 RNA < 40 copies/mL at 48 weeks.

And doctor, I want to point out that the results I just mentioned were reductions in viral load measured at < 40 copies/mL. That is a more stringent endpoint than you may have previously seen in clinical studies.

In summary, you can expect the same results in patients for whom you prescribe once daily ISENTRESS 600 mg tomorrow as those for whom you prescribed ISENTRESS 400 mg BID yesterday.

Coaching Tips



Listen for the following as the representative asks questions to IDENTIFY or CONFIRM the customer's needs:

- Focused, concise question(s) designed to identify or confirm the physician's thoughts on viral suppression in his/her current patients who are being treated with ISENTRESS 400 mg parentheses (once the rep has confirmed the physician's thoughts on viral suppression, has the rep transitioned to reinforcing this benefit with ISENTRESS 600 mg?)
 - Was the representative able to uncover the physician's expectations regarding viral suppression provided by HIV therapies?

Listen for the following as the representative SHARES key messages:

- Strong statement of the key message.
- Simple, brief explanation of the ONCEMRK study design and the efficacy data that supports once-daily dosing.
- Statement linking clinical results experienced with ISENTRESS 400 mg in the past to what the physician can expect with ISENTRESS 600 mg going forward.



ONCE DAILY ONCEMRK 48-WEEK DATA

Isentress 600_{mg}
raltegravir, MSD
For once-daily dosing at 1200 mg (2 x 600 mg)

Proven efficacy comparable with ISENTRESS¹

Robust viral suppression¹

Percentage of patients with HIV-1 RNA <40 copies/mL at 48 weeks (NG=F approach)¹

88.9%
ISENRESS 600 mg + TDF/FTC (n=531)

88.3%
ISENRESS + TDF/FTC (n=266)

ONCEMRK STUDY DESIGN

Randomized, double-blind, active-controlled superiority study in treatment-naïve HIV-infected patients ≥18 years of age with HIV RNA <1,000 copies/mL to evaluate the safety and antiretroviral activity of ISENTRESS 600 mg (at 1200 mg [2 x 600 mg] once daily) + TDF/FTC (n=531) vs ISENTRESS 400 mg twice daily + TDF/FTC (n=266). The primary end point was proportionally adjusted by the percentage of patients with HIV RNA <40 copies/mL at Week 48. A secondary end point was change from baseline in CD4 cell count at 48 weeks.

Insert appropriate Indications and local Selected Safety Information (SSI) for ISENTRESS and/or ISENTRESS 600 mg, as applicable, here.
The current global SSI can be found here: editorial.merck.com

Effective viral suppression regardless of baseline viral load

Percentage of patients with HIV-1 RNA <40 copies/mL at 48 weeks (OF approach)

>100,000 HIV-1 RNA copies/mL at baseline		≤100,000 HIV-1 RNA copies/mL at baseline	
ISENRESS 600 mg + TDF/FTC (n=331)	ISENRESS + TDF/FTC (n=266)	ISENRESS 600 mg + TDF/FTC (n=331)	ISENRESS + TDF/FTC (n=266)
86.7%	83.8%	97.2%	97.7%

OF = observed failure (baseline values carried forward for patients who discontinued due to lack of efficacy).

Similar increases in CD4 count

Mean change from baseline in CD4 cell count at 48 weeks (OF approach)

ISENRESS 600 mg + TDF/FTC (n=531)	ISENRESS + TDF/FTC (n=266)
+232	+234

Baseline CD4 cell count was ≥350 cells/mm³ for ISENTRESS 600 mg + TDF/FTC vs ≥300 cells/mm³ for ISENTRESS + TDF/FTC.
OF = observed failure (baseline values carried forward for patients who discontinued due to lack of efficacy).
A ISENTRESS 600 mg + ISENTRESS (95% CI) = -2 (-31, 4271)

Virologic and immunologic efficacy were similar to ISENTRESS irrespective of¹:

- Hepatitis B coinfection status
- Hepatitis C coinfection status
- Baseline CD4 cell count
- Gender
- Race/ethnicity
- Geographic region

CD4 = cluster of differentiation 4; CI = confidence interval; FTC = emtricitabine; HIV-1 = human immunodeficiency virus type 1; RNA = ribonucleic acid; TDF = tenofovir disoproxil fumarate.

Insight:

The efficacy results in ONCEMRK are solid. Make sure to emphasize that the efficacy results for ISENTRESS 600 mg were comparable to those of ISENTRESS regardless of baseline viral load, coinfection, baseline CD-4 cell count, gender, race, or ethnicity.

Identify & Confirm

Ask open-ended, thought-provoking questions about the physician's experience prescribing ISENTRESS 400 mg in a diverse patient population.

VERBALIZATION

Share Information

Use the right page of the second spread to engage the customer in a discussion of the comparable efficacy demonstrated in ONCEMRK across its diverse patient population.

VERBALIZATION

COACHING GUIDE

Identify and Confirm



Doctor, how are you treating your treatment-naïve patients who have comorbidities such as CNS, renal impairment, cardiovascular, HCV coinfection and polypharmacy type patients? What challenges do you face in treating these patients?

[NOTE: Pick one of these comorbidities to focus on during the interaction so you can ask for a simple, reasonable call to action.]

Share Information



Doctor, ISENTRESS 600 mg provides effective viral suppression comparable to ISENTRESS regardless of baseline viral load. At week 48 of the ONCEMRK study, 86.7% of patients in the ISENTRESS 600 mg group, who had greater than 100,000 HIV-1 RNA copies/mL at baseline, attained HIV-1 RNA <40 copies/mL, compared to 83.8% of patients in the ISENTRESS mg group.

And ISENTRESS 600 mg provided similar increases in CD4 count to those of ISENTRESS as well— 232 and 234 TDF/FTC, respectively.

In the ONCEMRK study, the virologic and immunologic efficacy of ISENTRESS 600 mg were similar to ISENTRESS irrespective of hepatitis B coinfection status, hepatitis C coinfection status, baseline CD4 cell count, gender, race/ethnicity, or geographic region.

Doctor, no matter how challenging the patient, ISENTRESS 600 mg once daily provides proven efficacy comparable with ISENTRESS.

[NOTE: If the doctor responds to your patient types question, skip to Spread 3 or 4 to discuss tolerability and the common HIV medications that can be used in combination with ISENTRESS 600 mg.]

Coaching Tips



Listen for the following as the representative asks questions to IDENTIFY or CONFIRM the customer's needs:

- Clear, concise questions designed to identify the opportunity in a prioritized treatment naïve plus 1 comorbidity patient type.
 - Once the representative identified the opportunity, did he/she ask additional open-ended, thought-provoking questions to understand how the physician is currently treating the treatment naïve plus 1 comorbidity patient?

Listen for the following as the representative SHARES key messages:

- Strong statement of the key message.
- Concise enumeration of the multiple ways in which comparable efficacy was demonstrated in ONCEMRK across its diverse patient population.

ONCE DAILY
ONCEMRK
48-WEEK DATA

Isentress 600_{mg}
raltegravir, MSD
For once-daily dosing at 1200 mg (2 x 600 mg)

Demonstrated tolerability comparable with ISENTRESS¹

No drug-related moderate to severe clinical adverse events occurred at a rate of $\geq 2\%$ in either treatment group through 48 weeks¹.

The most commonly reported clinical adverse events with ISENTRESS 600 mg and ISENTRESS (>10% in either treatment group), of all intensities and regardless of causality, respectively, were headache (13.4% vs 10.9%), nausea (11.3% vs 9.8%), and diarrhea (10.9% vs 11.3%).¹

F10 = emtricitabine; TDF = tenofovir disoproxil fumarate.

Insert local Selected Safety Information (SSI) for ISENTRESS and/or ISENTRESS 600 mg, as applicable, here. The current global SSI can be found here: editorial.merck.com.

<1% discontinuation rate for clinical or lab adverse events¹

Rates of discontinuation of therapy through 48 weeks in treatment-naïve patients¹

	ISENTRESS 600 mg + TDF/FTC (n=531)	ISENTRESS + TDF/FTC (n=266)
Due to clinical adverse event:	0.8%	2.3%
Due to laboratory adverse event:	0.4%	0.0%

Insight:

ISENTRESS is already well known for its tolerability, and the ONCEMRK safety results demonstrate comparable tolerability for ISENTRESS 600 mg.

Identify & Confirm

Ask open-ended, thought-provoking questions about the physician's experience of the tolerability of ISENTRESS in his/her practice.

VERBALIZATION

Share Information

Use the third and fourth spreads to highlight the ONCEMRK safety and tolerability data.

VERBALIZATION

COACHING GUIDE

Identify and Confirm



What has been your clinical experience when it comes to your patients' tolerability of ISENTRESS?

Doctor, how do you manage tolerability issues that may occur with other treatment regimens?

Share Information



...I am glad to hear that your patients on ISENTRESS have not experienced many tolerability issues. And now, Doctor, ISENTRESS 600 mg with once-daily dosing has demonstrated tolerability comparable with ISENTRESS.

In ONCEMRK, no drug-related moderate to severe clinical adverse events occurred at a rate of $\geq 2\%$ in either treatment group through 48 weeks. The most commonly reported clinical adverse events with ISENTRESS 600 mg and ISENTRESS (greater than 10% in either treatment group), of all intensities and regardless of cause, respectively, were headache (13.4% vs 10.9%), nausea (11.3% vs 9.8%), and diarrhea (10.9% vs 11.3%).

And the discontinuation rate for clinical or lab adverse events was less than 1% in the ISENTRESS 600 mg plus TDF/FTC treatment group through 48 weeks.

Doctor, you can expect the same tolerability with ISENTRESS 600 mg once daily as your patients have experienced with ISENTRESS 400 mg BID, for all these years.

Coaching Tips



Listen for the following as the representative asks questions to IDENTIFY or CONFIRM the customer's needs:

- Has the representative asked an open-ended, thought-provoking question to uncover a clinical experience that can be used throughout the conversation?

Listen for the following as the representative SHARES key messages:

- Clear statement of the key message.
 - Has the representative reinforced the clinical experience shared by the physician with relevant key messages?
 - Has the representative related the tolerability issues experienced by the physician with other treatments, to data confirming why they occur, and transitioned to the key messages showing the lack of DDIs with ISENTRESS 600 mg?
- Highlights of the ONCEMRK safety and tolerability data.
- Statement linking clinical results experienced with ISENTRESS 400 mg in the past to what the physician can expect with ISENTRESS 600 mg going forward.

Primarily metabolized through the UGT1A1 pathway

DRUG METABOLISM

CYP450 pathway	UGT1A1 pathway
Other integrase inhibitors are at least partially metabolized by CYP450 enzymes ^{1A}	Raltegravir is the only integrase inhibitor metabolized mainly by the UGT1A1 pathway without CYP450 contribution

Approximately 80% of drugs are metabolized by enzymes in the CYP450 pathway?

Inhibition or induction of CYP450 enzymes can cause⁸:

- Clinically significant drug interactions
- Unanticipated adverse reactions
- Therapeutic failures

Metabolism by a non-CYP pathway is less likely to precipitate drug interactions⁹

RIDS = acquired immune deficiency syndrome, ARV = antiretroviral, CV = cardiovascular, CYP = cytochrome P, CYP450 = cytochrome P450 enzyme, GEND = gastroesophageal reflux disease, GI = gastrointestinal, HCV = hepatitis C virus, PJP = pneumocystis jirovecii pneumonia, UCT = uric acid phosphate glucuronidation/transferase.

Insert local Selected Safety Information (SSI) for ISENTRESS and/or ISENTRESS 600 mg, as applicable, here.
The current global SSI can be found here: editorial.merck.com

Can be used with a range of medications^{10,a}

	ISENTRESS 600 mg	ISENTRESS
AIDS-related complications	✓	✓
Glucocorticoids	✓	✓
Anxiety/depression/pain	✓	✓
Miscellaneous opioid analgesics	✓	✓
Contraception	✓	✓
Hormonal contraceptives	✓	✓
CV/metabolic disorders	✓	✓
Progesterone, statins	✓	✓
Erectile dysfunction	✓	✓
Anti-erectile dysfunction agents	✓	✓
GI complications	✓	✓
Proton pump inhibitors	✓	✓
HCV direct-acting antivirals ^b	✓	✓
<small>Elastinase/paracetamol, ombitasvir/paritaprevir/ritonavir (used with or without dasabuvir), sofosbuvir, sofosbuvir/ledipasvir, sofosbuvir/velpatasvir</small>	✓	✓
Opportunistic infections	✓	✓
Acute anti-fungals	✓	✓
Substance abuse	✓	✓
Methadone	✓	✓
Tuberculosis	✗	✓ ^c
Ritonavir	✗	✓
ARVs	✗	✓
Abacavir or zidovudine	✗	✓
Antacids	✗	✓
Calcium carbonate-containing antacids	✗	✓
Aluminum- or magnesium-containing antacids	✗	✗

^aOther not clinically meaningful effect or no expected effect on pharmacokinetics.
^britonavir reduces plasma levels of raltegravir. If coadministration with ritonavir is unavoidable, a loading of the dose of raltegravir (1200 mg twice daily) can be considered. The impact of other strong inducers of drug-metabolizing enzymes, such as phenytoin and phenobarbital, on UGT1A1 is unknown; therefore, coadministration with raltegravir 1200 mg once daily is not recommended.

Share Information

The fourth spread continues the tolerability story. Use the left page of the fourth spread to discuss how ISENTRESS 600 mg is metabolized.

VERBALIZATION

Close

One call option is to reinforce the physician's tolerability experience with this page and then ask for a commitment.

VERBALIZATION

COACHING GUIDE

Insight:

The Drug Metabolism image at the top depicts the high proportion of drugs that are at least partially metabolized by the CYP450 pathway in comparison to ISENTRESS 600 mg. Remember, ISENTRESS is the only HIV therapy metabolized mainly by the UGT1A1 pathway *without* CYP450 contribution.

The drug metabolism of ISENTRESS provides a rationale for the favorable safety profile of ISENTRESS.

Share Information



Doctor, are you aware that approximately 80% of drugs are metabolized by enzymes in the CYP450 pathway? 80%! As you may know, inhibition or induction of CYP450 enzymes can cause clinically significant drug interactions, unanticipated adverse reactions, and even therapeutic failures. Metabolism by a non-CYP pathway is less likely to precipitate drug interactions. This may be one of the reasons ISENTRESS is well tolerated by many patients.

Close



Doctor, considering all the positive clinical experience you have had with ISENTRESS 400 mg BID – the proven efficacy that your patients have experienced year after year and the reliable tolerability that you get from an agent metabolized by a non-CYP pathway – will you consider prescribing ISENTRESS 600 mg for (INSERT TREATMENT NAÏVE PLUS 1 COMORBIDITY PATIENT TYPE) who would benefit from the added convenience of once-daily dosing?

Coaching Tips



Listen for the following as the representative SHARES key messages:

- Strong statement regarding the percentage of drugs metabolized by enzymes in the CYP450 pathway.
- Concise summary of the adverse effects of agents metabolized by enzymes in the CYP450 pathway.
- Clear differentiation of benefits of metabolism by a non-CYP pathway.
- Statement linking metabolism of ISENTRESS 600 mg to patient tolerability.

Listen for the following as the representative CLOSES the call and AGREES on next steps:

- Gains agreement on the information that was just shared regarding the benefits of the CYP450 pathway.
- Asks the customer for a commitment to prescribe ISENTRESS 600 mg for a prioritized treatment naïve plus 1 comorbidity patient type.
- Gets an agreement for follow-up.

Primarily metabolized through the UGT1A1 pathway

CYP450 pathway

Other integrase inhibitors are at least partially metabolized by CYP450 enzymes^{1,4}

UGT1A1 pathway

Raltegravir is the only integrase inhibitor metabolized mainly by the UGT1A1 pathway without CYP450 contribution

Approximately 80% of drugs are metabolized by enzymes in the CYP450 pathway⁵

Inhibition or induction of CYP450 enzymes can cause⁶:

- Clinically significant drug interactions
- Unanticipated adverse reactions
- Therapeutic failures

Metabolism by a non-CYP pathway is less likely to precipitate drug interactions⁷

ARDS = acquired immune deficiency syndrome; ARV = antiretroviral; CV = cardiovascular; CYP = cytochrome P; CYP450 = cytochrome P450 enzyme; GIRD = gastrointestinal reflux disease; GI = gastrointestinal; HIV = human immunodeficiency virus; PJP = pneumocystis jirovecii pneumonia; UGT = uridine diphosphate glucosyltransferase enzyme.

Insert local Selected Safety Information (SSI) for ISENTRESS and/or ISENTRESS 600 mg, as applicable, here. The current global SSI can be found here: editorial.merck.com

Isentress 600_{mg} raltegravir, MSD

Can be used with a range of medications^{10,a}

	ISENTRESS 600 mg	ISENTRESS
AIDS-related complications		
Glucocorticoids	✓	✓
Anxiety/depression/pain		
Mixazolam, opioid analgesics	✓	✓
Contraception		
Hormonal contraceptives	✓	✓
CV/metabolic disorders		
Pioglitazone, statins	✓	✓
Erectile dysfunction		
Anti-erectile dysfunction agents	✓	✓
GI complications		
Proton pump inhibitors	✓	✓
HCV direct-acting antivirals^b		
Eloprevir/sofosbuvir, ombitasvir/paritaprevir/ritonavir (used with or without dasabuvir), sofosbuvir, sofosbuvir/ledipasvir, sofosbuvir/velpatasvir	✓	✓
Opportunistic infections		
Azole antifungals	✓	✓
Substance abuse		
Medication	✓	✓
Tuberculosis		
Rifampicin	✗	✓ ^c
ARVs		
Atazanavir or tipranavir/ritonavir	✗	✓
Antacids		
Calcium carbonate-containing antacids	✗	✓
Aluminum- or magnesium-containing antacids	✗	✗

^aNeither a clinically meaningful effect nor an expected effect on pharmacokinetics.

^bYohimbinic reduces plasma levels of raltegravir. If coadministration with raltegravir is unavoidable, a 50% reduction of the dose of raltegravir (300 mg twice daily) can be considered. The impact of other strong inducers of drug-metabolizing enzymes, such as phenytoin and phenobarbital, on UGT1A1 is unknown; therefore, coadministration with raltegravir 1200 mg once daily is not recommended.

Insight:

While ISENTRESS 600 mg is comparable to ISENTRESS and can be used with a wide range of medications, there are a few exceptions. Be transparent about the medications that can not be used in combination with ISENTRESS 600 mg. You don't want to appear to be hiding unfavorable details and risk losing your customer's trust.

Identify & Confirm

Ask open-ended, thought-provoking questions leading the HCP into a conversation about the prioritized patient types.

VERBALIZATION

Share Information

Use the right page of the fourth spread to share the common HIV medications that can be used in combination with ISENTRESS 600 mg.

VERBALIZATION

Close

One call option is to reinforce the physician's tolerability experience with the fourth spread and then ask for a commitment to one or more specific patient types.

VERBALIZATION

COACHING GUIDE

Identify and Confirm



*Doctor, what are the factors you consider when choosing treatment for your treatment-naïve, **CNS** HIV patients?*

*How are you treating your treatment-naïve HIV patients with **renal impairment**?*

*How are you treating your treatment-naïve HIV patients with **cardiovascular** disease?*

*How are you treating your treatment-naïve HIV patients with **HCV coinfection**?*

*How are you treating your treatment-naïve HIV patients with **polypharmacy** issues?*

[NOTE: Pick one of these comorbidities to focus on during the interaction so you can ask for a simple, reasonable call to action.]

Share Information



Doctor, treating HIV-related complications can be complicated enough without worrying about which medications can and can't be used with your preferred HIV therapy.

Like ISENTRESS, ISENTRESS 600 mg can be used with a range of commonly prescribed HIV medications, such as glucocorticosteroids, proton pump inhibitors, and HCV direct-acting antivirals, used to treat HIV-related complications.

[NOTE: If the physician answers your Identify and Confirm question(s) with a response that includes a competitive product, address the differences between the products at this point.]

However, I need to draw your attention to a few exceptions that you may have been prescribing in combination with ISENTRESS in the past. ISENTRESS 600 mg should not be used in combination with rifampin, ARVs (such as, atazanavir or tipranavir/ritonavir), or calcium carbonate-, aluminum-, or magnesium-containing antacids.

Close



Doctor, based on the information I shared with you, would you agree that ISENTRESS 600 mg may be a better choice for your:

- treatment-naïve HIV patients with **CNS** issues?
- treatment-naïve HIV patients with **renal impairment**?
- treatment-naïve HIV patients with **cardiovascular** disease?
- treatment-naïve HIV patients with **HCV coinfection**?
- treatment-naïve, **polypharmacy** HIV patients?

Great! Will you start your treatment-naïve patients with (INSERT TREATMENT NAÏVE PLUS 1 COMORBIDITY PATIENT TYPE) on ISENTRESS 600 mg?

May I follow up with you in a few weeks to discuss these new starts?

Coaching Tips



Listen for the following as the representative asks questions to IDENTIFY or CONFIRM the customer's needs:

- Open-ended, thought-provoking question(s) leading the HCP into a conversation about the prioritized patient types.
 - Uncovers beliefs about how the prescriber is treating that specific treatment naïve plus 1 comorbidity patient type and why.
 - Effectively "changes the conversation" and focuses on the treatment naïve plus 1 comorbidity patient type.

Listen for the following as the representative SHARES key messages:

- Outlines the range of common HIV medications that can be used in combination with ISENTRESS 600 mg.
- Describes the few drugs that interact with ISENTRESS 600 mg.
- Effectively differentiates between ISENTRESS 600 mg and the competitor (if the prescriber shared a preferred competitor).

Listen for the following as the representative CLOSES the call and AGREES on next steps:

- Gains agreement on the information that was just shared regarding the efficacy, tolerability and range of common HIV medications that can be used in combination with ISENTRESS 600 mg.
- Asks the customer for a commitment to prescribe ISENTRESS 600 mg for a prioritized treatment naïve plus 1 comorbidity patient type.
- Gets an agreement for follow-up.

Offer the efficacy and tolerability of ISENTRESS 600 mg—with the added convenience of once-daily dosing

Adult dosing recommendations

<p>Isentress 600_{mg} raltegravir, MSD</p> <ul style="list-style-type: none"> ✓ Treatment-naïve patients ✓ Patients who are virologically suppressed on an initial regimen of ISENTRESS 400 mg twice daily <p>ONCE DAILY</p> <p>at 1200 mg (2 x 600 mg)</p> <p><small>Tablets shown at actual size.</small></p>	<p>ISENTRESS raltegravir, MSD</p> <ul style="list-style-type: none"> ✓ Treatment-naïve patients ✓ Treatment-experienced patients <p>TWICE DAILY</p> <p>400 mg + 400 mg</p> <p><small>Tablets shown at actual size.</small></p>
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The 400-mg tablet should not be used to administer 1200-mg once-daily regimen

Other considerations

<p>Booster-free</p>	<p>Can be administered with or without food</p>
<p>No dosage adjustment is required for patients with mild to moderate hepatic impairment*</p> <p><small>*The hepatic impairment study has been conducted with ISENTRESS 1200 mg (2 x 600 mg) once daily. However, based on results with ISENTRESS 400 mg twice-daily tablet, no clinically meaningful effect is expected for mild and moderate hepatic impairment. The effect of severe hepatic insufficiency on the pharmacokinetics of raltegravir has not been studied.</small></p>	<p>No dosage adjustment is required for patients with renal impairment*</p> <p><small>*The renal impairment study was conducted with ISENTRESS 1200 mg (2 x 600 mg) once daily. However, based on results with ISENTRESS 400 mg twice-daily tablet, no clinically meaningful effect is anticipated. Because the extent to which raltegravir may be dialyzable is unknown, dosing before a dialysis session should be avoided.</small></p>

Insert local Selected Safety Information (SSI) for ISENTRESS and/or ISENTRESS 600 mg, as applicable, here. The current global SSI can be found here: editorial.merck.com

Insight:

Spread 5 is a great opportunity to guide the physician into a conversation around once-daily dosing of ISENTRESS 600 mg.

Identify & Confirm

Ask open-ended, thought-provoking questions about the physician's thoughts on the convenience of once-daily dosing.

VERBALIZATION

Share Information

Use the left page of the fourth spread to discuss how ISENTRESS 600 mg once daily and ISENTRESS 400 mg BID are dosed.

VERBALIZATION

COACHING GUIDE

Identify and Confirm



How do your patients feel about once-daily dosing?

How do you feel about now having the option of once-daily dosing along with the proven efficacy and tolerability in ISENTRESS 600 mg?

How is this going to change how you treat your patients?

Share Information



Now you can offer your patients the efficacy and tolerability of ISENTRESS 600 mg—with the added convenience of once-daily dosing.

Most likely, you already have patients on ISENTRESS 400 mg, which is for both treatment-naïve and treatment-experienced patients. These patients are currently taking one 400-mg tablet twice daily for a total daily dose of 800 mg.

Now you can offer ISENTRESS 600 mg for your treatment-naïve plus 1 comorbidity patients or your patients who are already virologically suppressed on an initial regimen of ISENTRESS 400 mg twice daily. These patients will take two 600-mg tablets once daily for a total daily dose of 1200 mg.

And doctor, it is not recommended to substitute the 400-mg tablet for the 600-mg tablet to create a 1200-mg once-daily dose because there are differences in the pharmacokinetic profile.

Coaching Tips



Listen for the following as the representative asks questions to IDENTIFY or CONFIRM the customer's needs:

- Clear, concise questions designed to identify or confirm the physician's thoughts on the convenience of once-daily dosing.
 - Did the representative learn or uncover how the prescriber is going to change his future prescribing habits?
 - If the prescriber isn't going to change their habits, what else does the representative need to ask or share?

Listen for the following as the representative SHARES key messages:

- Relevant information based on the customer's response.
- Strong statement of the key message.
- Clear differentiation between the dosing and total daily dose of ISENTRESS 400 mg and that of ISENTRESS 600 mg.
- Caution around substituting 3 X 400 mg for 2 X 600 mg once daily.

Offer the efficacy and tolerability of ISENTRESS 600 mg—with the added convenience of once-daily dosing

Adult dosing recommendations

<p>Isentress 600_{mg} raltegravir, MSD</p> <ul style="list-style-type: none"> ✓ Treatment-naïve patients ✓ Patients who are virologically suppressed on an initial regimen of ISENTRESS 400 mg twice daily <p>ONCE DAILY</p> <p>at 1200 mg (2 x 600 mg)</p> <p><small>Tablets shown at actual size.</small></p>	<p>ISENTRESS_{600mg}</p> <ul style="list-style-type: none"> ✓ Treatment-naïve patients ✓ Treatment-experienced patients <p>TWICE DAILY</p> <p>400 mg + 400 mg</p> <p><small>Tablets shown at actual size.</small></p>
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The 400-mg tablet should not be used to administer 1200-mg once-daily regimen

Other considerations

<p>Booster-free</p>	<p>Can be administered with or without food</p>
<p>No dosage adjustment is required for patients with mild to moderate hepatic impairment*</p> <p><small>*The hepatic impairment study has been conducted with ISENTRESS 1200 mg (2 x 600 mg) once daily. However, based on results with ISENTRESS 400 mg twice-daily tablet, no clinically meaningful effect is expected for mild and moderate hepatic impairment. The effect of severe hepatic dysfunction on the pharmacokinetics of raltegravir has not been studied.</small></p>	<p>No dosage adjustment is required for patients with renal impairment†</p> <p><small>†No renal impairment study was conducted with ISENTRESS 1200 mg (2 x 600 mg) once daily. However, based on results with ISENTRESS 400 mg twice-daily tablet, no clinically meaningful effect is anticipated. Because the subject to which raltegravir may be dispensed is unknown, dosing before a dialysis session should be avoided.</small></p>

Insert local Selected Safety Information (SSI) for ISENTRESS and/or ISENTRESS 600 mg, as applicable, here. The current global SSI can be found here: [editorial.merck.com](#)

Insight:
This page provides a great opportunity to engage the physician in a discussion around patients with comorbidities.

Identify & Confirm

Ask open-ended, thought-provoking questions about other convenience factors that your physician may consider important.

VERBALIZATION

Share Information

Use the right page of the fifth spread to share additional considerations with ISENTRESS 600 mg.

VERBALIZATION

Close

One call option is to use this spread to discuss the HIV patient with comorbidities and then ask for a commitment.

VERBALIZATION

COACHING GUIDE

Identify and Confirm



Doctor, what other factors do you and your patients consider to be important in relation to the “convenience” of a drug regimen?

Doctor share with me, what are some of the challenges you face in prescribing therapies for your HIV patients with CNS (OR, INSERT DIFFERENT COMORBIDITY)?

How do you identify treatment-naïve patients who have comorbidities and thus may need to be on a tailored regimen?

Share Information



Doctor, ISENTRESS 600 mg is booster-free and can be taken with or without food.

In addition, no dosage adjustments are required for patients with renal impairment or with mild to moderate hepatic impairment.

All in all, ISENTRESS 600 mg may be more convenient for your patients to take.

Close



Doctor, considering all the advantages of prescribing ISENTRESS 600 mg as an HIV therapy that provides durable efficacy, is well tolerated, and has few drug-to-drug interactions, will you consider prescribing ISENTRESS 600 mg for appropriate treatment-naïve HIV patients with (INSERT TREATMENT NAÏVE PLUS 1 COMORBIDITY PATIENT TYPE) in your practice?

[NOTE: Close on the comorbidity that you focused on during the interaction so you can ask for a simple, reasonable call to action.]

Coaching Tips



Listen for the following as the representative asks questions to IDENTIFY or CONFIRM the customer's needs:

- Clear, concise questions to identify or confirm other convenience factors that the physician may consider important.
 - Did the representative uncover the customer's challenges?

Listen for the following as the representative SHARES key messages:

- Descriptive summary of the other factors that the physician may take into consideration when selecting an HIV therapy.
- Confirmation of the benefits to both the physician and patient of other convenience factors associated with ISENTRESS 600 mg.

Listen for the following as the representative CLOSES the call and AGREES on next steps:

- Gains agreement on the information that was just shared regarding the other convenience factors with ISENTRESS 600 mg.
- Asks the customer for a commitment to prescribe ISENTRESS 600 mg for the prioritized treatment naïve plus 1 comorbidity patient type that was the focus of the call.
- Gets an agreement for follow-up.

TWICE DAILY
ACTG 5257
96-WEEK DATA

Superior efficacy + tolerability vs select PIs⁵

Lower rate of virologic failure⁵

Regimen	Cumulative Incidence (%)
ISENTRRESS + TDF/FTC (n=511)	9.0%
ATV + TDF/FTC (n=471)	12.6%
DRV + TDF/FTC (n=481)	14.9%

Lower rate of tolerability failure⁵

Regimen	Cumulative Incidence (%)
ISENTRRESS + TDF/FTC (n=511)	0.9%
ATV + TDF/FTC (n=471)	13.9%
DRV + TDF/FTC (n=471)	4.7%

Superior composite assessment of virologic efficacy and tolerability⁵

Regimen	Cumulative Incidence (%)
ISENTRRESS + TDF/FTC (n=511)	8.6%
ATV + TDF/FTC (n=471)	24.1%
DRV + TDF/FTC (n=471)	16.6%

ACTG 5257 STUDY DESIGN
Randomized, open-label, active-controlled equivalence study of 1,800 treatment-naïve adults with HIV-1 RNA >1,000 copies/mL, 24% non-Hispanic Black, 34% non-Hispanic white, 22% Hispanic; 24% women randomized 1:1:1 to ISENTRESS 600 mg BID + TDF/FTC or ATV 300 mg QD + TDF/FTC or DRV 600 mg QD + TDF/FTC. The primary end points were virologic failure, defined as confirmed HIV-1 RNA level >1,000 copies/mL from week 12 to before Week 24 or >200 copies/mL at or after Week 24, and time to tolerability failure, defined as the time from randomization to discontinuation of ISENTRESS, ATV, or DRV for toxicity. A composite composite and joint was defined as the earlier occurrence of virologic failure or tolerability failure. Key inclusion criteria included no prior ARV treatment and no genotypic resistance to NRTIs and PIs. Limitations: The trial was open label. Blinding was not provided, although copy reimbursements were provided where allowed for use. Experience was predefined as a 2-sided 97.5% CI on the pairwise difference in 96-week cumulative incidence of each individual or composite end point (split between -10% and +10%).⁵

All 3 study regimens yielded equivalent rates of virologic suppression over 96 Weeks. At 96 weeks, 94% of patients on the ISENTRESS regimen had HIV-1 RNA levels <50 copies/mL, compared with 85% on DRV and 92% on ATV.⁵

ATV = atazanavir; CI = confidence interval; DRV = dolutegravir; FTC = emtricitabine; HIV-1 = human immunodeficiency virus type 1; NRTI = nucleoside reverse transcriptase inhibitor; PI = protease inhibitor; RNA = ribonucleic acid; TDF = tenofovir disoproxil fumarate.

1% of patients on the ISENTRESS regimen discontinued for toxicity compared with 5% on DRV and 16% on ATV.⁵

ISENTRRESS was superior to both ATV and DRV in the predefined cumulative composite and joint of virologic failure and tolerability failure.⁵

Insert local Selected Safety Information (SSI) for ISENTRESS and/or ISENTRESS 600 mg, as applicable, here.
The current global SSI can be found here: editorial.merck.com

Insert local Selected Safety Information (SSI) for ISENTRESS and/or ISENTRESS 600 mg, as applicable, here.
The current global SSI can be found here: editorial.merck.com

Insight:

Note the banner across the top of the page – this spread provides a head-to-head comparison between select protease inhibitors (PI) and ISENTRESS 400 mg BID.

This is an opportunity to remind physicians that while PIs are highly respected for their efficacy profile, the ACTG 5257 study demonstrated that ISENTRESS 400 mg BID provides a superior composite assessment of virologic efficacy and tolerability compared to select PIs.

Identify & Confirm

Ask open-ended, thought-provoking questions about the physician's perception of protease inhibitors.

VERBALIZATION

Share Information

Use the sixth spread to share the superior composite efficacy and tolerability profile of ISENTRESS 400 mg versus select protease inhibitors (PI) with physicians who may prefer to prescribe PIs.

VERBALIZATION

Close

One call option is to use this spread to address the physician's perspective on PIs versus ISENTRESS and then ask for a commitment.

VERBALIZATION

COACHING GUIDE

Identify and Confirm



Doctor, share your thought process with me; in what patient type would you use a protease inhibitor? Why?

Doctor, what protease inhibitors do you currently prescribe? What do you like about protease inhibitors?

Share Information



Doctor, I think you'd agree that PIs are highly respected for their efficacy profile. However, the ACTG 5257 study demonstrated that ISENTRESS 400 mg BID provides a superior composite assessment of virologic efficacy and tolerability compared to select PIs. The ACTG study showed equivalent virologic failure between treatment groups. Only the composite endpoint was superior.

Close



Doctor, you have agreed that ISENTRESS 400 mg provides a superior composite assessment of virologic efficacy and tolerability compared with select PIs.

Will you consider prescribing ISENTRESS 600 mg with the added advantage of once-daily dosing for your treatment-naïve HIV patients with (INSERT TREATMENT NAÏVE PLUS 1 COMORBIDITY PATIENT TYPE) instead of the (INSERT COMPETITOR NAME) you currently prescribe?



Coaching Tips

Listen for the following as the representative asks questions to IDENTIFY or CONFIRM the customer's needs:

- Clear, concise questions designed to identify or confirm the physician's use of protease inhibitors in his/her practice.
 - Did the representative identify the opportunity in a specific treatment naïve plus 1 comorbidity patient type?
 - Has the representative uncovered the physician's preferred PI and what he/she likes about it?

Listen for the following as the representative SHARES key messages:

- Strong description of the superior composite efficacy and tolerability profile of ISENTRESS 400 mg versus select protease inhibitors (PI).

Listen for the following as the representative CLOSES the call and AGREES on next steps:

- Gains agreement on the information that was just shared regarding a superior composite assessment of virologic efficacy and tolerability with ISENTRESS 600 mg compared with select PIs.
- Ask physician to switch from their preferred protease inhibitor to ISENTRESS 600 mg for the specific patient type focused on during the interaction.
- Gets an agreement for follow-up.

TWICE DAILY
STARTMRK
240-WEEK DATA

Durable efficacy and tolerability through 5 years vs an NNRTI²

Sustained viral suppression²

HIV-1 RNA <50 copies/mL (NCF approach)²

• Suppression was demonstrated at all time points. In addition, superiority was shown at weeks 192 and 240 in prespecified superiority analyses.²

Week	ISENTRESS + TDF/FTC (n=281)	EFV + TDF/FTC (n=282)
8	86%	82%
32	86%	82%
48	81%	79%
60	81%	79%
72	81%	79%
84	81%	79%
96	81%	79%
108	75%	69%
120	75%	69%
132	75%	69%
144	75%	69%
156	76%	67%
168	76%	67%
180	76%	67%
192	76%	67%
204	76%	67%
216	76%	67%
228	71%	61%
240	71%	61%

The primary end point was noninferiority with respect to the percentage of patients with HIV-1 RNA <50 copies/mL at Week 48. NCF: Patients who discontinued treatment regardless of reason were considered failures thereafter. Δ ISENTRESS-EFV (95% CI) = +0.9 (-1.7, +3.7-3). P<0.001 for noninferiority at all time points. Copyright © 2014 Lipincott Williams & Wilkins.

High immunologic response^{2,12}

Mean change from baseline in CD4 cell count at Week 240 (OF approach)

ISENTRESS + TDF/FTC (n=281)	EFV + TDF/FTC (n=282)
+374	+312

Baseline CD4 cell count was 219 cells/mm³ for ISENTRESS + TDF/FTC vs 217 cells/mm³ for EFV + TDF/FTC. Observed failure (OF) analysis: Patients who discontinued treatment because of lack of efficacy were considered failures thereafter. Similar results were observed with the NCF approach. Δ ISENTRESS-EFV (95% CI) = +62 (-22, +102).

Demonstrated tolerability profile

Drug-related clinical adverse events occurring in ≥5% of the study populations

	ISENTRESS + TDF/FTC (n=281)	EFV + TDF/FTC (n=282)
Diarrhea	5.3%	9.9%
Flatulence	3.6%	5.0%
Nausea	8.9%	11.0%
Fatigue	4.3%	8.9%
Dizziness	7.8%	35.3%
Headache	9.3%	14.2%
Somnolence	1.1%	7.4%
Abnormal dreams	6.8%	13.3%
Insomnia	7.5%	8.2%
Nightmare	2.8%	5.3%
Rash	1.1%	8.2%

Includes adverse experiences at least possibly, probably, or definitely related to the drug.

Low discontinuations due to adverse events²

ISENTRESS + TDF/FTC (n=281)	EFV + TDF/FTC (n=282)
5%	10%

ART = antiretroviral therapy; CD4 = cluster of differentiation 4; CI = confidence interval; EFV = efavirenz; FTC = zidovudine; HIV-1 = human immunodeficiency virus type 1; NNRTI = non-nucleoside reverse transcriptase inhibitor; RNA = ribonucleic acid; TDF = tenofovir disoproxil fumarate.

STARTMRK STUDY DESIGN

Randomized, double-blind, active-controlled superiority study in treatment-naïve adult patients ≥18 years of age with HIV-1. To evaluate the safety and ART activity of ISENTRESS 600 mg twice daily + TDF 300 mg/FTC 200 mg (n=281) vs EFV 600 mg + TDF 300 mg/FTC 200 mg (n=282). The primary end point was noninferiority with respect to the percentage of patients with HIV-1 RNA <50 copies/mL at Week 48, with a secondary end point of 96 weeks. Prespecified superiority analyses examined results at Weeks 156, 192, and 240. Formal hypothesis testing was not performed at Weeks 156, 192, and 240. Key inclusion criteria were susceptibility to TDF, FTC, and FTC at entry on prior ART; HIV-1 RNA >5,000 copies/mL, without genotypic resistance to TDF, FTC, or EFV.²

Insight:

You should be very familiar with this data as STARTMRK was the original study used to support the ISENTRESS 400 mg indication in treatment-naïve patients. It isn't necessary to provide a traditional detail on the STARTMRK data as you introduce ISENTRESS 600 mg. Instead focus on the message that ISENTRESS is the only integrase inhibitor with long-term efficacy of 5 years demonstrated in clinical trials.

Identify & Confirm

Ask open-ended, thought-provoking questions about the physician's perception of the duration of efficacy of ISENTRESS.

VERBALIZATION

Share Information

Use the seventh spread to highlight the durable efficacy and tolerability through 5 years with ISENTRESS 400 mg BID vs an NNRTI.

VERBALIZATION

COACHING GUIDE

Identify and Confirm



Doctor, what has been your clinical experience of the duration of efficacy and tolerability of ISENTRESS?

Share Information



Doctor, I don't know if you're aware of it but ISENTRESS is the only integrase inhibitor with long-term efficacy of 5 years demonstrated in clinical trials.

The STARTMRK study compared the durable efficacy and tolerability of ISENTRESS 400 mg BID to an NNRTI over a 240-week period. Over the 5 years of the study, ISENTRESS provided sustained viral suppression, high immunologic response, with a demonstrated tolerability profile and low discontinuation due to adverse events.

These data suggest that your patients may continue to experience the proven efficacy and tolerability of ISENTRESS year after year.

Coaching Tips



Listen for the following as the representative asks questions to IDENTIFY or CONFIRM the customer's needs:

- Focused questions designed to identify or confirm the physician's perceptions of the duration of efficacy of ISENTRESS.
 - Was the representative able to engage the customer in a discussion of their clinical experience?

Listen for the following as the representative SHARES key messages:

- Compelling messaging highlighting the durable efficacy and tolerability through 5 years of ISENTRESS 400 mg BID vs an NNRTI that was demonstrated in STARTMRK.
- If the representative was able to engage the customer in a discussion of their clinical experience, was he/she able to reinforce the customer's clinical experience with the key messages?



Close



Use the back cover to summarize all the features and benefits that your customer has appreciated with ISENTRESS 400 mg BID, now with the added convenience of once-daily dosing. Then, close with a call to action.

VERBALIZATION

COACHING GUIDE

Insight:
Use the back cover to explore the various patients in your customer's practice appropriate for ISENTRESS 600 mg once daily.

Close



Doctor, all the features you have appreciated with ISENTRESS 400 mg BID – the 10 years of proven experience, the proven efficacy in treatment-naïve adults, long-term efficacy of 5 years demonstrated in clinical trials, and demonstrated tolerability – are available in ISENTRESS 600 mg, with the added convenience of once-daily dosing.

Doctor, I know you have had great clinical experience with ISENTRESS, and you agreed that ISENTRESS 600 mg may be a convenient choice for your (INSERT TREATMENT NAÏVE PLUS 1 COMORBIDITY PATIENT TYPE); will you choose a regimen with ISENTRESS 600 mg for those patients?

Coaching Tips



Listen for the following as the representative CLOSES the call and AGREES on next steps:

- Gains agreement on the information that was just shared regarding the features and benefits that your customer has appreciated with ISENTRESS 400 mg BID, now with the added convenience of once-daily dosing.
- Asks the customer for a commitment to prescribe ISENTRESS 600 mg for the prioritized treatment naïve plus 1 comorbidity patient type that was the focus of the call.
- Gets an agreement for follow-up.

MSD Selling Model: Customer Focused Interaction CFI

