

Initial REMS Approval: 09/25/2009
Most Recent Modification: 05/2012

BLA 125261 STELARA[®] (ustekinumab)

Human interleukin 12 and 23 antagonist

RISK EVALUATION AND MITIGATION STRATEGY (REMS)

I. GOALS

To evaluate and mitigate the potential risks of serious infections and malignancy, and reversible posterior leukoencephalopathy syndrome (RPLS) associated with STELARA[®] by:

- alerting and warning healthcare providers about the risks

II. REMS ELEMENTS

A. COMMUNICATION PLAN

Janssen Biotech, Inc. will implement a communication plan to the following healthcare providers:

- Dermatologists and dermatology healthcare providers (HCPs) who are likely to prescribe and/or inject STELARA[®]
- Oncologists who may treat malignancies potentially associated with the use of immunosuppressants for chronic inflammatory and autoimmune disease and will need to ascertain cases of malignancy after a long latency period
- Rheumatologists who may co-manage with dermatologists moderate to severe psoriasis patients with psoriatic arthritis
- Infectious disease specialists and gastroenterologists who may be consulted about infections and will need to understand the potential for infectious complications of IL-12/IL-23 blockade
- Neurologists who may treat RPLS

The communication plan will provide for the dissemination of risk information about serious infection, malignancy, and RPLS.

Elements of the communication plan:

1. A Dear Healthcare Professional letter (see Attachment A) will be distributed to dermatologists, oncologists, rheumatologists, infectious disease specialists, gastroenterologists, and neurologists within 60 days of STELARA[®] initial approval.

2. A Dear Pharmacist letter (see Attachment B) will be distributed to pharmacists within 60 days of STELARA[®] initial approval.
3. Dissemination of information about serious infection, malignancy, and RPLS to health care providers through certain dermatology, oncology, rheumatology, infectious diseases, and gastroenterology professional societies' journals:
 - 1) For display as a panel/poster and distribution as printed material at all dermatology and oncology scientific meetings where the company has a sponsored booth
 - 2) For quarterly presentation as a printed information piece in the *Journal of the American Academy of Dermatology* and the *Archives of Dermatology* for 3 years from initial approval
 - 3) For quarterly presentation as a printed information piece in the *Journal of Clinical Oncology* and *Blood* for 5 years from initial approval
 - 4) For twice yearly presentation as a printed information piece in *Arthritis and Rheumatism*, the *Journal of Infectious Disease*, the *American Journal of Gastroenterology*, and *Gastroenterology* for 3 years from initial approval

The REMS Journal Information Piece is appended to this document (see Attachments C, D, E, F, and G).

4. Janssen Biotech, Inc. will ensure that all materials listed in or appended to the STELARA REMS program will be available through the STELARA REMS program website www.stelarainfo.com/hcp/remes/stelara/index.html. This information will remain on the website for a period of 5 years from initial approval.

The STELARA REMS program website landing page is appended to this document (see Attachment H).

B. TIMETABLE FOR SUBMISSION OF ASSESSMENTS

Janssen Biotech, Inc. will submit REMS assessments to FDA 18 months, 3 years, and 7 years from the initial date of the approval (September 25, 2009) of the REMS. To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 days before the submission date for that assessment. Janssen Biotech, Inc. will submit each assessment so that it will be received by the FDA on or before the due date.

Attachment A Dear Healthcare Professional Letter



Dear Healthcare Professional:

The purpose of this letter is to inform you of important safety information for STELARA[®] (ustekinumab), a human monoclonal antibody which has been approved by the Food and Drug Administration (FDA) for the treatment of adult patients (18 years or older) with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy. STELARA[®] targets interleukin-12 (IL-12) and interleukin-23 (IL-23).

FDA has determined that a Risk Evaluation and Mitigation Strategy (REMS) is necessary for STELARA[®] to ensure that the benefits of the drug outweigh the potential risks of serious infections and malignancy, and reversible posterior leukoencephalopathy syndrome (RPLS).

IMPORTANT SAFETY INFORMATION FOR POTENTIAL RISKS OF SERIOUS INFECTIONS AND MALIGNANCIES, AND RPLS

The following information is important for healthcare professionals and patients treated with STELARA[®]:

Infections

- STELARA[®] may increase the risk of infections and reactivation of latent infections. Serious bacterial, fungal, and viral infections, some requiring hospitalization, were observed in patients receiving STELARA[®]. STELARA[®] should not be given to patients with a clinically important active infection and should not be administered until the infection resolves or is adequately treated. Instruct patients to seek medical advice if signs or symptoms suggestive of an infection occur. Exercise caution when considering use of STELARA[®] in patients with a chronic infection or a history of recurrent infection.

Theoretical Risk for Vulnerability to Particular Infections

- Individuals genetically deficient in IL-12/IL-23 are particularly vulnerable to disseminated infections from mycobacteria, salmonella, and *Bacillus Calmette-Guerin* (BCG) vaccinations. Serious infections and fatal outcomes have been reported in such patients.

- It is not known whether patients with pharmacologic blockade of IL-12/IL-23 from treatment with STELARA[®] will be susceptible to these types of infections. Appropriate diagnostic testing should be considered as dictated by clinical circumstances.

Pre-Treatment Evaluation of Tuberculosis (TB)

- Evaluate patients for TB infection prior to initiating treatment with STELARA[®]. Do not administer STELARA[®] to patients with active TB. Initiate treatment of latent TB before administering STELARA[®].
- Consider anti-tuberculosis therapy prior to initiation of STELARA[®] in patients with a past history of latent or active tuberculosis in whom an adequate course of treatment cannot be confirmed.
- Patients receiving STELARA[®] should be monitored closely for signs and symptoms of active TB during and after treatment.

Malignancies

- STELARA[®] (ustekinumab) is an immunosuppressant and may increase the risk of malignancy. Malignancies were reported among subjects who received STELARA[®] in clinical studies.
- The safety of STELARA[®] has not been evaluated in patients who have a history of malignancy or who have a known malignancy.

Reversible Posterior Leukoencephalopathy Syndrome (RPLS)

- One case of RPLS has been reported in a STELARA[®]-treated subject.
- RPLS is a neurological disorder, which is not caused by demyelination or a known infectious agent. RPLS can present with headache, seizures, confusion and visual disturbances. It has been associated with preeclampsia, eclampsia, acute hypertension, cytotoxic agents and immunosuppressive therapy.
- If RPLS is suspected, discontinue STELARA[®] and administer appropriate treatment.

Reporting Patient Adverse Events

It is important that you report all serious adverse events that occur in patients using STELARA[®]. If you have a patient who develops a serious infection or RPLS while being treated with STELARA[®], or if you have a patient with cancer at any time after receiving STELARA[®] therapy, it is important that you report the case even if you do not think there is a causal relationship.

The information that you can provide may inform therapy and monitoring decisions for psoriasis patients.

Reporting is easy and maintains patient confidentiality. Your patient's name or contact information is not needed. *HIPAA does not apply* to this adverse event reporting.

You can report your cases to the STELARA[®] manufacturer or directly to FDA.

- Janssen Biotech, Inc. at 1-800-526-7736
- MedWatch (FDA safety information and adverse event reporting program) at 1-800-332-1088 or online at www.fda.gov/medwatch/report.htm

VOLUNTARY REGISTRY INFORMATION

PSOLAR (PSoriasis Longitudinal Assessment and Registry) is a Janssen Biotech, Inc. -sponsored voluntary psoriasis registry that will be available to enroll patients treated with STELARA[®]. Please call 1-888 PSOLAR-5 or go to www.clinicaltrials.gov for more information.

Please see the enclosed:

- STELARA[®] package insert, and
- Medication Guide

Please Note: This letter does not include a comprehensive description of the serious and significant risks associated with the use of STELARA[®]. Please read the accompanying Full Prescribing Information and Medication Guide for a complete description of the serious and significant risk that may be associated with the use of STELARA[®]. You are advised to discuss the risks that may be associated with STELARA[®] therapy with patients and their caregivers. We have enclosed a copy of the STELARA[®] Medication Guide, which is required to be provided to patients with every filled prescription. This Medication Guide contains information that can be used to facilitate discussions about the potential risks of therapy.

Sincerely,

Peter Callegari, MD
Vice President, Medical Affairs

Enclosures

Attachment B Dear Pharmacist Letter



Dear Pharmacist:

The purpose of this letter is to inform you of important safety information for STELARA[®] (ustekinumab), a human monoclonal antibody which has been approved by the Food and Drug Administration (FDA) for the treatment of adult patients (18 years or older) with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy. STELARA[®] targets interleukin-12 (IL-12) and interleukin-23 (IL-23). FDA has determined that a Risk Evaluation and Mitigation Strategy (REMS) is necessary for STELARA[®] to ensure that the benefits of the drug outweigh the potential risks of serious infections and malignancy, and reversible posterior leukoencephalopathy syndrome (RPLS).

FDA requires that a copy of the enclosed STELARA[®] Medication Guide be distributed to each patient (or agent such as a caregiver) who fills a prescription for STELARA[®]. A copy of the STELARA[®] Medication Guide will be packaged with every vial of STELARA[®].

Should you require additional copies of the STELARA[®] Medication Guide, you may

- Request copies from Janssen Biotech, Inc. by calling the toll-free medical information line at 1-800-526-7736
- Print copies of the Medication Guide from the STELARA[®] website www.stelarainfo.com
- Request copies from your drug supplier
- Photocopy the enclosed Medication Guide, after confirming that it is the most current version
- Call the toll-free medical information line at the number above

IMPORTANT SAFETY INFORMATION FOR POTENTIAL RISKS OF SERIOUS INFECTIONS AND MALIGNANCIES, AND RPLS

Important Safety Information is listed in the Warnings and Precautions sections of the Prescribing Information for STELARA[®] and Medication Guide for patients.

Infections

- STELARA[®] may increase the risk of infections and reactivation of latent infections. Serious bacterial, fungal, and viral infections, some requiring hospitalization, were observed in patients receiving STELARA[®]. STELARA[®] should not be given to patients with a clinically important active infection and should not be administered until the infection resolves or is adequately treated. Instruct patients to seek medical advice if signs or symptoms suggestive of an infection occur. Exercise caution when considering use of STELARA[®] in patients with a chronic infection or a history of recurrent infection.

Theoretical Risk for Vulnerability to Particular Infections

- Individuals genetically deficient in IL-12/IL-23 are particularly vulnerable to disseminated infections from mycobacteria, salmonella, and *Bacillus Calmette-Guerin* (BCG) vaccinations. Serious infections and fatal outcomes have been reported in such patients.
- It is not known whether patients with pharmacologic blockade of IL-12/IL-23 from treatment with STELARA[®] (ustekinumab) will be susceptible to these types of infections. Appropriate diagnostic testing should be considered as dictated by clinical circumstances.

Pre-Treatment Evaluation of Tuberculosis (TB)

- Evaluate patients for TB infection prior to initiating treatment with STELARA[®]. Do not administer STELARA[®] to patients with active TB. Initiate treatment of latent TB before administering STELARA[®].
- Consider anti-tuberculosis therapy prior to initiation of STELARA[®] in patients with a past history of latent or active tuberculosis in whom an adequate course of treatment cannot be confirmed.
- Patients receiving STELARA[®] should be monitored closely for signs and symptoms of active TB during and after treatment.

Malignancies

- STELARA[®] is an immunosuppressant and may increase the risk of malignancy. Malignancies were reported among subjects who received STELARA[®] in clinical studies.
- The safety of STELARA[®] has not been evaluated in patients who have a history of malignancy or who have a known malignancy.

Reversible Posterior Leukoencephalopathy Syndrome (RPLS)

- One case of RPLS has been reported in a STELARA[®]-treated subject.
- RPLS is a neurological disorder, which is not caused by demyelination or a known infectious agent. RPLS can present with headache, seizures, confusion and visual disturbances. It has been associated with preeclampsia, eclampsia, acute hypertension, cytotoxic agents and immunosuppressive therapy.

- If RPLS is suspected, discontinue STELARA[®] and administer appropriate treatment.

REPORTING PATIENT ADVERSE EVENTS

It is important that you report all serious adverse events that occur in patients using STELARA[®]. If you are aware of a patient who develops a serious infection or RPLS while being treated with STELARA[®], or if you are aware of a patient with cancer at any time after receiving STELARA[®] therapy, it is important that you report the case even if you do not think there is a causal relationship. The information that you can provide may inform therapy and monitoring decisions.

Reporting is easy and maintains patient confidentiality. The patient's name or contact information is not needed. *HIPAA does not apply* to this adverse event reporting.

You can report cases to the STELARA[®] manufacturer or directly to FDA.

- Janssen Biotech, Inc. at 1-800-526-7736
- MedWatch (FDA safety information and adverse event reporting program) at 1-800-332-1088 or online at www.fda.gov/medwatch/report.htm

Please Note: This letter does not include a comprehensive description of the serious and significant risks that may be associated with the use of STELARA[®]. Please read the accompanying Full Prescribing Information and Medication Guide for a complete description of the serious and significant risk that may be associated with the use of STELARA[®].

Sincerely,

Peter Callegari, MD
Vice President, Medical Affairs
Enclosures

Attachment C Journal Information Piece for Dermatologists

Important Information for Dermatologists about the Potential Risks of Serious Infections and Malignancy, and RPLS with STELARA™ for Psoriasis Therapy

STELARA® (ustekinumab) is a human monoclonal antibody that is indicated for the treatment of adult patients (18 years or older) with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy.

STELARA® targets interleukin-12 (IL-12) and interleukin-23 (IL-23). Based on data from rodent models and humans genetically deficient for components of IL-12 and IL-23 pathways, there is a theoretical concern that **blockade of IL-12 and IL-23 may increase the risk for serious infections, including mycobacterial and recurrent salmonella infections**. In addition, data from rodent models suggest there is a theoretical concern that **blockade of IL-12 and IL-23 may increase the risk for malignancies**.

One case of Reversible Posterior Leukoencephalopathy Syndrome (RPLS) has been reported in a STELARA®-treated patient in clinical trials. RPLS is a neurological disorder which is not caused by demyelination or a known infectious agent, and can present with headache, seizures, confusion and visual disturbances.

If you have a patient that develops a serious infection or RPLS while being treated with STELARA®, or if you have a patient with cancer at any time after receiving STELARA® therapy, it is important that you report the case even if you do not think there is a causal relationship.

The information that you, as a STELARA® prescribing dermatologist, can provide may inform therapy and monitoring decisions for psoriasis patients.

Reporting is easy and maintains patient confidentiality. Your patient's name or contact information is not needed. *HIPAA does not apply* to this adverse event reporting.

You can report your cases to the STELARA® manufacturer or directly to FDA.

- Janssen Biotech, Inc. at 1-800-526-7736
- MedWatch (FDA safety information and adverse event reporting program) at 1-800-332-1088 or online at www.fda.gov/medwatch/report.htm

PSOLAR (Psoriasis Longitudinal Assessment and Registry): is a **voluntary, disease specific registry**, developed by Janssen Biotech, Inc. that collects information from psoriasis patients and their treating physicians. Since this registry will continue for 10 years, it will help us better understand the risk of long-latency serious events, such as malignancies, that can occur after exposure to a product such as STELARA®.

For more information on PSOLAR and how to include patients in this voluntary registry, call 1-888-PSOLAR5 (1-888-776-5275) or access www.clinicaltrials.gov and search for PSOLAR.

**Important Information for Oncologists
About Potential Malignancy Risk
With STELARA™ for Psoriasis Therapy**

STELARA® (ustekinumab) is a human monoclonal antibody that is indicated for the treatment of adult patients (18 years or older) with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy.

STELARA® targets interleukin-12 (IL-12) and interleukin-23 (IL-23). Based on data from rodent models, there is a theoretical concern that **blockade of IL-12 and IL-23 may increase the risk for malignancies.**

If you are consulted to see a patient with cancer at any time after receiving STELARA® therapy, it is important that you report the case even if you do not think there is a causal relationship.

The information that you, as an oncologist, can provide may inform therapy and monitoring decisions for psoriasis patients.

Reporting is easy and maintains patient confidentiality. Your patient's name or contact information is not needed. *HIPAA does not apply* to this adverse event reporting.

You can report your cases to the STELARA® manufacturer or directly to FDA.

- Janssen Biotech, Inc. at 1-800-526-7736
- MedWatch (FDA safety information and adverse event reporting program) at 1-800-332-1088 or online at www.fda.gov/medwatch/report.htm

Attachment E Journal Information Piece for Rheumatologists

Important Information for Rheumatologists about the Potential Risks of Serious Infections and Malignancy, and RPLS with STELARA™ for Psoriasis Therapy

STELARA® (ustekinumab) is a human monoclonal antibody that is indicated for the treatment of adult patients (18 years or older) with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy.

STELARA® targets interleukin-12 (IL-12) and interleukin-23 (IL-23). Based on data from rodent models and humans genetically deficient for components of IL-12 and IL-23 pathways, there is a theoretical concern that **blockade of IL-12 and IL-23 may increase the risk for serious infections, including mycobacterial and recurrent salmonella infections.** In addition, data from rodent models suggest there is a theoretical concern that **blockade of IL-12 and IL-23 may increase the risk for malignancies.**

One case of Reversible Posterior Leukoencephalopathy Syndrome (RPLS) has been reported in a STELARA®-treated patient in clinical trials. RPLS is a neurological disorder which is not caused by demyelination or a known infectious agent, and can present with headache, seizures, confusion and visual disturbances.

If you have a patient that develops a serious infection or RPLS while being treated with STELARA®, or if you have a patient with cancer at any time after receiving STELARA® therapy, it is important that you report the case even if you do not think there is a causal relationship.

The information that you, as a rheumatologist that may co-manage patients receiving STELARA® therapy, can provide may inform therapy and monitoring decisions for psoriasis patients.

Reporting is easy and maintains patient confidentiality. Your patient's name or contact information is not needed. *HIPAA does not apply to this adverse event reporting.*

You can report your cases to the STELARA® manufacturer or directly to FDA.

- Janssen Biotech, Inc. at 1-800-526-7736
- MedWatch (FDA safety information and adverse event reporting program) at 1-800-332-1088 or online at www.fda.gov/medwatch/report.htm

**Important Information for Infectious Disease Specialists
About Potential Serious Infection Risk
With STELARA™ for Psoriasis Therapy**

STELARA® (ustekinumab) is a human monoclonal antibody that is indicated for the treatment of adult patients (18 years or older) with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy.

STELARA® targets interleukin-12 (IL-12) and interleukin-23 (IL-23). Based on data from rodent models and humans genetically deficient for components of IL-12 and IL-23 pathways, there is a theoretical concern that **blockade of IL-12 and IL-23 may increase the risk for serious infections, including mycobacterial and recurrent salmonella infections.**

If you are consulted to see a patient that develops a serious infection while being treated with STELARA®, it is important that you report the case even if you do not think there is a causal relationship.

The information that you, as an infectious disease specialist, can provide may inform therapy and monitoring decisions for psoriasis patients.

Reporting is easy and maintains patient confidentiality. Your patient's name or contact information is not needed. *HIPAA does not apply* to this adverse event reporting.

You can report your cases to the STELARA® manufacturer or directly to FDA.

- Janssen Biotech, Inc. at 1-800-526-7736
- MedWatch (FDA safety information and adverse event reporting program) at 1-800-332-1088 or online at www.fda.gov/medwatch/report.htm

Attachment G Journal Information Piece for Gastroenterologists

Important Information for Gastroenterologists About Potential Serious Infection Risk With STELARA™ for Psoriasis Therapy

STELARA® (ustekinumab) is a human monoclonal antibody that is indicated for the treatment of adult patients (18 years or older) with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy.

STELARA® targets interleukin-12 (IL-12) and interleukin-23 (IL-23). Based on data from rodent models and humans genetically deficient for components of IL-12 and IL-23 pathways, there is a theoretical concern that **blockade of IL-12 and IL-23 may increase the risk for serious infections, including mycobacterial and recurrent salmonella infections.**

If you are consulted to see a patient that develops a serious infection while being treated with STELARA®, it is important that you report the case even if you do not think there is a causal relationship.

The information that you, as a gastroenterologist, can provide may inform therapy and monitoring decisions for psoriasis patients.

Reporting is easy and maintains patient confidentiality. Your patient's name or contact information is not needed. *HIPAA does not apply* to this adverse event reporting.

You can report your cases to the STELARA® manufacturer or directly to FDA.

- Janssen Biotech, Inc. at 1-800-526-7736
- MedWatch (FDA safety information and adverse event reporting program) at 1-800-332-1088 or online at www.fda.gov/medwatch/report.htm

Attachment H STELARA REMS Program Website Landing Page

Risk Evaluation and Mitigation Strategy (REMS)

At Janssen Biotech, Inc., we understand our responsibility to provide knowledge and resources to help ensure continuous safety monitoring and the timely identification and reporting of adverse events. We recognize the importance of education as the foundation of informed Benefit:Risk decisions and this website is dedicated to communicating important safety information about STELARA[®] to contribute to those decisions.

One method that the FDA can use to convey important safety information about products with known, or potential, serious risks is through a communication plan within a Risk Evaluation and Mitigation Strategy (REMS). A REMS is an overall strategy that focuses on managing risks associated with a drug or biological product.

Janssen Biotech, Inc. has worked with the FDA to develop a program to communicate important safety information about STELARA[®]. All biologic therapies carry with them certain risks that warrant your consideration prior to initiation of therapy. The goal of this REMS is to communicate and mitigate the risks associated with STELARA[®] by alerting healthcare professionals and patients about the potential risks of serious infections and malignancy, and Reversible Posterior Leukoencephalopathy Syndrome (RPLS).

Janssen Biotech, Inc. has provided information within this website to increase healthcare professionals' and patients' awareness of these risks. Please review all materials to help ensure that the most informed conversations can occur and to facilitate appropriate utilization of STELARA[®].

IMPORTANT HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use STELARA[®] safely and effectively. See full prescribing information for STELARA[®].

WARNINGS AND PRECAUTIONS

- **Infections:** Serious infections have occurred. Do not start STELARA[®] during any clinically important active infection. If a serious infection develops, stop STELARA[®] until the infection resolves. (See Section 5.1 of the Prescribing Information)
- **Theoretical Risk for Particular Infections:** Serious infections from mycobacteria, salmonella and Bacillus Calmette-Guerin (BCG) vaccinations have been reported in patients genetically deficient in IL-12/IL-23. Diagnostic tests for these infections should be considered as dictated by clinical circumstances. (See Section 5.2 of the Prescribing Information)
- **Tuberculosis (TB) evaluation:** Evaluate patients for TB prior to initiating treatment with STELARA[®]. Initiate treatment of latent TB before administering STELARA[®]. (See Section 5.3 of the Prescribing Information)

- Malignancies: STELARA[®] may increase risk of malignancy. The safety of STELARA[®] in patients with a history of or a known malignancy has not been evaluated. (See Section 5.4 of the Prescribing Information)
- Reversible Posterior Leukoencephalopathy Syndrome (RPLS): One case was reported. If suspected, treat promptly and discontinue STELARA[®]. (See Section 5.5 of the Prescribing Information)

ADVERSE REACTIONS

Most common adverse reactions (incidence >3% and greater than with placebo): Nasopharyngitis, upper respiratory tract infection, headache, and fatigue. (See Section 6.1 of the Prescribing Information)

To report SUSPECTED ADVERSE REACTIONS, contact Janssen Biotech, Inc. at 1-800-526-7736 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Live vaccines: Should not be given with STELARA[®]. (See Section 7.1 of the Prescribing Information)
- Concomitant therapy: The safety of concomitant use of STELARA[®] with immunosuppressants or phototherapy has not been evaluated. (See Section 7.2 of the Prescribing Information)

Please see accompanying Full Prescribing Information and Medication Guide for STELARA[®]

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

TATIANA OUSSOVA
05/02/2012