TYSABRI
Risk Management Plan

Carmen Bozic, MD
Vice President
Drug Safety and Risk Management
Biogen Idec Inc
Presentation Outline

♦ Overview and Goals of Plan
♦ Risk Minimization Plan
♦ Risk Assessment Plan
♦ Evaluation of Plan
♦ Benefit-Risk Considerations
TYSABRI Risk Management Plan Development

♦ Based on FDA Guidance document and ongoing dialogue with FDA
♦ Present updated version of plan
♦ Careful review of risk management plans with other drugs
TYSABRI Risk Management Plan Development

- Developed based on feedback from many neurologists, infusion nurses, and MS patients
  - Neurology expert panels and advisory boards
  - Infusion nurse and MS patient focus groups and surveys
- Minimize risk without creating unintended consequences that may obstruct patient access
TYSABRI Risk Management Goals

♦ Risk Minimization Goals
  – Promote informed benefit-risk decisions
  – Minimize the risk of PML
  – Potentially minimize death and disability due to PML

♦ Risk Assessment Goals
  – Determine the incidence and risk factors for PML
  – Assess long-term safety in clinical practice

Evaluation and Enhancements
Risk Minimization Plan
Important Features of TYSABRI Treatment

- Monthly infusions by healthcare professional
- Prescribed by small group of neurology specialists
- Neurologists best qualified specialists to manage PML
Risk Minimization Plan

- Revised Labeling
- Risk Minimization System
TYSABRI Revised Labeling: Key Concepts in New Boxed Warning

- TYSABRI is associated with increased risk of PML which causes death or severe disability
- Warn against concurrent use with immunosuppressants (eg, azathioprine) or immunomodulators (eg, interferon-beta)
- Indicated *only* for relapsing MS
- Healthcare professionals should be alert to any signs or symptoms that may be suggestive of PML
  - Dosing should be suspended immediately at the first signs or symptoms suggestive of PML
  - Evaluation should include brain MRI and CSF for JC viral DNA
TYSABRI Revised Labeling: Additional Warnings

- An MRI scan should be obtained prior to initiating TYSABRI
- Contraindicated in patients who are immunocompromised
Risk Minimization Plan

- Revised Labeling
- Risk Minimization System
TYSABRI Risk Minimization System

- Mandatory Enrollment Form
- TYSABRI Registry
- Controlled Centralized Distribution
- Registered Infusion Centers

Neurologists
Infusion Nurses
MS Patients
Patient-Physician Acknowledgement on Enrollment Form

♦ Records informed benefit-risk decision before start of therapy

♦ Physician signs:
  – Is aware of PML risk
  – Has discussed risks and benefits with patient
  – Patient appropriate for TYSABRI

♦ Patient signs:
  – Has read Medication Guide
  – Has discussed risks and benefits with physician
  – Will report new or worsening neurological symptoms to their physician
Infusion Center Requirements

♦ TYSABRI use only in registered infusion centers
  – Educational training of infusion nurses
  – Infusion center attests to follow risk management requirements
♦ Dosing only to patients enrolled in TYSABRI Registry
♦ Medication Guide to patient with every dose
♦ Documentation in TYSABRI Infusion Log
♦ Infusion centers will be audited by Biogen Idec

♦ Completion of Patient Checklist before each dose
Pre-Infusion Patient Checklist

- Designed based on feedback from neurologists
- Screens patient for new or worsening neurologic symptoms
  - If symptoms are detected, the physician will be immediately contacted and dosing will be suspended
- Administered prior to each infusion in each patient
  - By neurologist or neurologist’s nurse in office or by phone OR
  - By infusion nurse in infusion center
  - Appropriate for use in multiple clinical practice settings
- Facilitates close clinical follow-up of all patients
- Reinforces use as monotherapy and not in immunocompromised patients
**TYSABRI Risk Minimization System**

1. Physician’s office
2. Mandatory enrollment of Patient and Physician
3. Confirms enrolled Patient
4. Registered Infusion Center
5. TYSABRI shipment
6. Patient

**Biogen Idec**

**Registered Infusion Center**

**Controlled Centralized Distribution System**
Risk Assessment Plan
Commitment to Further Study TYSABRI Safety

Major Post-Marketing Studies
- TYSABRI Registry
- TYSABRI Observational Cohort Study

Additional Studies
- Re-dosing studies
- PML epidemiological studies
- Immune function study
- Non-clinical studies
TYSABRI Registry

Purpose:
To determine incidence and risk factors in TYSABRI-treated patients for PML and other serious opportunistic infections

♦ Mandatory enrollment of physicians and patients

♦ Physicians to report any PML event to Biogen Idec

♦ Physicians queried on every patient every 6 months on:
  – PML, other serious opportunistic infections, death of any cause, TYSABRI discontinuation
  – Patients remain in Registry for minimum 6 months after last dose

♦ Collect all spontaneously reported adverse events
TYSABRI Registry (Cont’d)

♦ Follow-up of patient deaths through National Death Index and collection of death certificates

♦ Non-compliance will result in “de-enrollment”

♦ Provides intense safety surveillance and tracking of all patients, far exceeding routine pharmacovigilance
TYSABRI Registry (Cont’d)

If PML occurs:

- Thorough data collection related to case
- Analysis of any PML case
- Pre-defined criteria for PML
- Expedited reporting to the FDA
- Ongoing assessment of benefit-risk
TYSABRI Observational Cohort Study

Purpose:
Evaluation of TYSABRI long-term safety in clinical practice setting

✦ Subset of patients in TYSABRI Registry will enroll into this voluntary observational cohort study
✦ 5000 MS patients worldwide (3000 in US) followed for 5 years
✦ Powered to detect rare events with incidence of 0.06%
✦ Collects all serious adverse events and concomitant immunomodulatory and immunosuppressant therapies
✦ Assess risk of serious infections and malignancies
✦ Investigate potential signals of unanticipated adverse events
Evaluation of Risk Management Plan
Evaluation of Risk Management Plan

- Monitor success of risk management plan
- Includes analysis of data from TYSABRI Registry
- Share data with FDA every 3 months
- If needed, implement rapid corrective actions
  - Labeling changes
  - Improvements in risk minimization system and tools
Summary:
TYSABRI Risk Management Plan

♦ Goals: To inform and minimize risk of PML
  – Mandatory registration of all prescribers and patients
  – Monthly screening of patients
  – Controlled, centralized distribution
  – Use only in registered infusion centers

♦ Ongoing assessment of PML risk and overall safety

♦ Evaluation plan to monitor success of risk management

♦ Appropriate use without unnecessary burden to physicians or barriers to patient access
Benefit-Risk Considerations
Benefit-Risk Considerations

♦ MS is a devastating, progressively disabling neurologic disease with high unmet need

♦ TYSABRI is a highly effective therapy

♦ Benefit consistent in broad range of sub-groups

♦ PML is a rare but serious risk

♦ Comprehensive risk management plan to minimize and assess this risk

♦ Favorable benefit-risk profile
Appropriate Use of TYSABRI

**Use Conditions**
Relapsing MS Patients:
- Only as monotherapy
- Not immunocompromised
- Enrolled in TYSABRI Registry
- Fully informed about PML risk

**Patient Selection**
Relapsing MS Patients:
- With disease activity on current therapy, or
- Intolerant of current therapy, or
- With high disease activity, or
- Others deemed appropriate based on individual benefit-risk assessment