Pediatric Focused Safety Review: adalimumab (Humira®)

Pediatric Advisory Committee Meeting
December 8, 2009

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Outline

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Background Drug Information

- **Drug:** adalimumab (Humira®)
- **Therapeutic Category:** tumor necrosis factor (TNF) blocker
- **Formulation:** subcutaneous injection
- **Sponsor:** Abbott Laboratories
- **Original Market Approval:** December 31, 2002
- **Indications (adult):** rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, Crohn's disease, plaque psoriasis

Background Drug Information

- **PREA Labeling Changes** (February 21, 2008):
  - Indication: patients 4-17 years with juvenile idiopathic arthritis (JIA)
  - Dosage in Pediatric Patients
    - 15 kg <30 kg : 20 mg every other week
    - ≥30 kg: 40 mg every other week
  - New dosage form (20 mg pre-filled syringe)

PREA Studies

adalimumab (Humira®)

Study of polyarticular JIA patients (4-17 years, n=171 exposed to adalimumab)

- Lead-in open-label phase
- Randomized, double-blind withdrawal phase of adalimumab compared to placebo for responders
- Open-label safety extension (Two arms: body surface area vs. fixed dosing regimen)

Efficacy established based on the primary endpoint, time to disease flare in the double-blind phase

PREA Studies, cont.

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Safety:

- Database (n=171): patients receiving adalimumab for >6 months (n=130), >1 year (n=126), >3 years (n=103)
- In general, adverse events similar in frequency and type to adults.
- Severe adverse events: neutropenia, streptococcal pharyngitis, increased aminotransferases, herpes zoster, myositis, metrorrhagia, appendicitis.
- Serious infections: 4% of patients within ~ 2 years of treatment initiation, included herpes simplex, pneumonia, urinary tract infection, pharyngitis and herpes zoster

PREA Studies, cont.

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Safety, cont:

- Differences from adults:
  - higher rate of hypersensitivity reactions (6% vs. 1% in adults)
  - higher rate of immunogenicity: development of antibodies to adalimumab (16% vs. 5% in adults)
  - creatinine phosphokinase elevation (15%)
  - myositis (n=1)
  - granuloma annulare (n=2)
  - “sporadic seizure” (n=1)
  - No deaths, malignancies, opportunistic or mycobacterial infections

PREA Labeling Changes

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- Indication (1.2)*
- Dosage and Administration (2.2)*
- Warnings and Precautions (5.10) : patients with JIA, immunizations should be up to date before initiating therapy
- Adverse Events (6.2):
  - adverse events similar to adult patients
  - important findings and differences from adults provided including granuloma annulare, elevation of creatinine phosphokinase and immunogenicity data

**Information provided in Highlights & Full Prescribing Information*

PREA Labeling Changes, cont.

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- Pediatric Use (8.4)
  - safety and efficacy in pediatric patients for use in indications other than JIA have not been established
  - approved JIA 4-17 years
  - limited data on patients <15 kg
- Pharmacokinetics (12.3)
  - pediatric steady-state trough data
- Clinical studies (14.2)
  - summary of the PREA study, including design and efficacy results
- Medication Guide (17.3)
  - approved in JIA patients >4 years

Additional Relevant Safety Labeling

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- Boxed Warning:
  - Serious Infections
    - Increased risk of serious infections leading to hospitalization or death, including tuberculosis (TB), bacterial sepsis, invasive fungal infections and infections due to other opportunistic pathogens
    - Test for latent TB, if positive start treatment before HUMIRA
    - Monitor patients for signs and symptoms of infection, including TB
  - Malignancy
    - “Lymphoma and other malignancies, some fatal, have been reported in children and adolescent patients treated with TNF blockers, of which HUMIRA is a member.”

Additional Relevant Safety Labeling, cont.

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- Warnings and Precautions*:
  - Serious Infections (5.1)
  - Malignancies (5.2)
  - Anaphylaxis/Hypersensitivity Reactions (5.3)
  - Hepatitis B virus reactivation (5.4)
  - Demyelinating disease (5.5)
  - Cytopenias (5.6)
  - Heart failure (5.8)
  - Lupus-like syndrome (5.9)

**Highlights and Full Prescribing Sections*

Additional Relevant Safety Labeling, cont.

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- Malignancies (5.2)
  - Adult
    - Clinical trial experience data provided
      - more cases of malignancy have been observed in adalimumab treated patients compared to controls in clinical trials
    - In controlled trials of all TNF blockers, more lymphoma cases observed in TNF blocker-treated patients
    - Postmarketing reports of acute and chronic leukemia in association with TNF-blocker use

Additional Relevant Safety Labeling, cont.

adalimumab (Humira®)

- Malignancies (5.2)
  - Pediatric
    - Malignancies, some fatal, have been reported among children, adolescents, and young adults who received treatment with TNF-blocking agents (initiation of therapy ≤ 18 years of age)
    - Lymphomas - ~50% of cases
    - Variety of malignancies-~50%
      - Includes rare malignancies associated with immunosuppression and malignancies not usually observed in children and adolescents.
    - Median treatment: 30 months (range 1-84 months)
    - Most patients on concomitant immunosuppressants

Additional Relevant Safety Labeling, cont.

adalimumab (Humira®)

Note: Pediatric malignancy information included in HUMIRA labeling changes November 2009

- Early Communication (June 4, 2008):
  - ongoing safety review of the TNF blockers and pediatric malignancies.
- FDA conclusion announced (August 4, 2009):
  - pediatric patients treated with TNF blockers are at increased risk of lymphoma and other malignancies, including types rarely seen in children, such as leiomyosarcoma, renal cell carcinoma and hepatic malignancies
  - all TNF blocker manufacturers to add a Boxed Warning for an increased risk of malignancy in children.

Postmarketing Requirements

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Pediatric JIA:

- Observational study/registry*
  - patients 4-17 years (n=800)
  - 10 year study with more intensive data collection during the first 5 years
- Safety/pharmacokinetic registry*
  - patients with JIA 2-4 years (n=30)
  - patients will be included in the observational study, i.e. safety data will be collected for 10 years (below)

**status: pending*

Postmarketing Requirements, cont.

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Adult:

- Provide safety data from 3 long-term (5 year) extension safety data of clinical trials of adults with RA *(status: data submitted)*
  Of note, Sponsor plans additional surveillance up to 10 years
- Pregnancy registry of patients on adalimumab with RA, 3 year study *(status: "delayed", but underway)*

The Sponsor of adalimumab has additional postmarketing requirements for other approved indications

Drug Use Trends

May 1, 2006 – April 30, 2009

- Total claims (all ages): ~1,000,000
  - Pediatric (0-16 years) claims: ~1% of total
- Unique patients (all ages): ~100,000
  - Pediatric patients (0-16 years) : ~1.5% of total
- Top prescribing specialty for pediatric patients:
  - Pediatrics (or pediatricians)
  - Pediatric Gastroenterology
  - Pediatric Rheumatology
- Top diagnosis code patients 0-16 years:
  - Regional Enteritis Unspecified Site (~52 % of claims)
  - Other Noninfectious Gastroenteritis (~24% of claims)
  - Rheumatoid arthritis (~22% of claims)

Data from Wolkers Kluwer SOURCE Lx ® database: 2006-2009, Extracted: August 2009

Adverse Event Reports since Market Approval

(December 31, 2002-July 7, 2009)

Crude counts*	All reports (US)	Serious** (US)	Death (US)
All ages	42,852 (34,889)	12,693 (5,148)	1,618 (658)
- Adults (> 17)	34,240 (27,759)	10,627 (4,410)	1,331 (539)
- Pediatrics (0-16)	471 (412)	128 (79)	4 (2)
- Unknown Age	8,141 (6,718)	1,938 (659)	283 (117)

*may include duplicates and unknown ages
**Serious AEs per regulatory definition (CFR 314.80) include death, life-threatening, hospitalization (initial or prolonged), disability & congenital anomaly

Adverse Event Reports, cont.

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- Serious Adverse Events (n=128)
  - Unique reports: n=109
  - All events labeled, except for some single reports noted under "Other category" (Slide 21)
  - Events related to *in utero* exposure: n=37
  - Events related to unapproved indications: n=51

    (n=42: Crohn's disease; n=3 ulcerative colitis; n=2: uveitis, psoriasis; n=1: psoriatic arthritis, vasculitis)
  - Death: n=4
    - Infants with history of *in utero* exposure n=3
    - 16 year old with interstitial pneumonia, pyrexia, productive cough and dyspnea died of respiratory failure; laboratories consistent with macrophage activation syndrome;11 month history of adalimumab use for JIA. Also treated with antibiotics and cyclosporine*.

**cyclosporine labeled for serious infection*

Adverse Event Reports, cont.

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- Non- Fatal Serious Adverse Events (n=105)
  - *In Utero* Exposure/Adverse Pregnancy Outcomes: n=34
  - Serious infection: n=24
    - Concomitant immunosuppressants n=11
    - Etiology:

      n=3: tuberculosis

      n=2: Staphylococcus*, cellulitis, “viral”

      n=1:Herpes zoster, cytomegalovirus, *C. difficile*, pneumonia, *Candida*, keratitis; n=9: unknown.

      **no species identified*

Adverse Event Reports, cont.

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– Disease Flares/Drug Ineffective: n=22

n=18: Crohn's disease*

n=2: JIA, Psoriasis*

**represent use for unapproved indications*

– Hypersensitivity/Injection site reactions: n=7**

- Events**: n=14 (n=3: injection site pain; n=2: diffuse swelling, pyrexia; n=9: single reports)

  ***some reports list more than one event*

- No reports of anaphylaxis or autoantibodies

Adverse Event Reports, cont.

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– Malignancy: lymphoma n=2

- 10 year old with JIA developed Hodgkin's lymphoma after adalimumab use for 2.4 years and methotrexate use for 3.7 years.
- 16 year old on abatacept for vasculitis, diagnosed with lymphomatoid papulosis and lymphoma. Patient had received adalimumab for 14 months beginning ~33 months before diagnosis.
- Both cases:
  - ~10 year use of immunosuppressants including products labeled for malignancy, i.e. methotrexate, rituximab, etanercept, infliximab, azathioprine and cyclophosphamide
  - outcome unknown

Adverse Event Reports, cont.

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- Other serious events (n=16)
  - n=3: chest pain*

    **chest pain is a labeled event*
  - n=1: single reports
    - One report of seizure in patient with uncontrolled diabetes. Diabetes felt to be cause of event.
    - One report of an 11 year old with muscle spasms. No laboratory data or noted concern of myositis.
- No reports of CPK elevation

Summary

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- Labeling has been updated to include a Boxed Warning and provide additional data under Warnings and Precautions about an increased risk of lymphoma and other malignancies in pediatric patients.

- The Sponsor has a postmarketing requirement to perform a 10 year safety study in 800 patients 4-17 years with JIA.

- The Sponsor has submitted data from 3 long-term (5 year) safety surveillance studies of adalimumab exposure in adults with RA and is required to establish a pregnancy registry of patients on anti-rheumatic therapy.

Summary, cont.

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- FDA recommends to continue routine, ongoing post-marketing safety monitoring for all adverse events.

- Does the committee concur?

ACKNOWLEDGEMENTS

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Eric Brodsky, MD
Joann Buenconsejo, PhD
Christopher Hilfiger
Larissa Lapteva, MD
Sarah Okada, MD
Dionne Price, PhD
Bob Rappaport, MD
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