Pediatric Focused Safety Review: Actemra® (tocilizumab) Pediatric Advisory Committee Meeting March 14, 2013

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Outline

- Background Information
- Pediatric Studies
- Relevant Labeling
- Drug Use Trends
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- Summary

Background Drug Information Actemra® (tocilizumab)

- **Drug:** Actemra® (tocilizumab)
- **Formulation:** injection for intravenous infusion.
- **Sponsor:** Genentech, Inc.
- **Original Market Approval:** January 8, 2010.
- **Pediatric Labeling Change:** April 15, 2011.
- **Therapeutic Category:** interleukin-6 (IL-6) receptor inhibitor.

Background Drug Information, continued
Actemra® (tocilizumab)

- **Indications:**

  1. Rheumatoid Arthritis - Adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response to one or more Disease-Modifying Anti-Rheumatic Drugs (DMARDs).

  2. Systemic Juvenile Idiopathic Arthritis (SJIA) – patients two years of age and older with active systemic juvenile arthritis.

- **Postmarketing Requirements:**

  Assessment of pharmacokinetic (PK/PD) parameters and dosing, efficacy, safety, tolerance and immunogenicity in the pediatric population ages ~ 2 years to < 17 years with polyarticular juvenile rheumatoid arthritis (JIA).

  A pharmacokinetic and safety study of tocilizumab (TCZ) in patients less than 2 years old with active systemic juvenile idiopathic arthritis (SJIA).

Systemic Juvenile Rheumatoid Arthritis (SJIA)*

- SJIA occurs in about 10% of patients with JIA.
- SJIA is defined as: Arthritis in one or more joints with or preceded by fever of at least 2 weeks' duration that is documented to be daily ("quotidian") for at least 3 days, and accompanied by one or more of the following:
  - Evanescent (nonfixed) erythematous rash
  - Generalized lymph node enlargement
  - Hepatomegaly and/or splenomegaly
  - Serositis
- Laboratory testing may not be helpful: rheumatoid factor (RF) is negative and anti-nuclear antibody (ANA) is positive in 10%.

*Petty, et al:. "ILAR classification of JIA." *The Journal of Rheumatology* (2004); 31; 390-392. and Cassidy JT, Petty RE. "Juvenile rheumatoid arthritis." In: Cassidy JT, Petty RE, editors. *Textbook of pediatric rheumatology.* Philadelphia: WB Saunders Company: 2001. p. 218–321.

Systemic Juvenile Rheumatoid Arthritis (SJIA), continued

- Differential diagnosis includes (but is not limited to) infection, malignancy, inflammatory bowel disease and connective tissue diseases.
- Course of disease and prognosis:
  - Half of the patients have persistent disease.
  - Systemic features subside over 2-5 years with joint involvement becoming the predominant feature.
  - Poor prognosis if multiple joints involved.
  - Persistent joint involvement can lead to permanent disability.
  - Death rate for SJIA is higher than that of other forms of JIA with one study showing 14 % of patients deceased at 15 years post diagnosis. When death occurs, it is most commonly attributed to infection.

Pediatric Studies
Actemra® (tocilizumab)

Pediatric data supporting SJIA indication:

- Randomized, double-blind, placebo-controlled 12 week trial (n=112, 2 to 17 years of age) with inadequate clinical response to non-steroidal anti-inflammatory drugs (NSAIDs) or corticosteroids.
  - 70% on methotrexate and 50% on corticosteroids at baseline.
  - Trial included an open-label extension up to five years with the bulk of patients completing 1 year. 109 patients were enrolled at week 24 and 103 patients at week 52.
- Studies conducted outside the US: 167 patients in short and long-term studies and 597 patients in postmarketing registries (as of May 15, 2010).

Pediatric Studies
Actemra® (tocilizumab)

Pediatric data supporting SJIA indication (continued):

- The most common adverse events in the 12 week controlled portion of the trial (incidence ≥ 5%) in pediatric patients treated with Actemra® were upper respiratory tract infection, headache, nasopharyngitis and diarrhea.
- Serious adverse events seen in the US clinical trial in patients on tocilizumab were macrophage activation syndrome (3%), infusion reactions (16%), anaphylaxis (<1%), immunogenicity (2%), decreased neutrophils (17%), decrease platelets (4%) and elevations of lipids (2%) and liver function tests (13%).
- There was 1 death in the US study and 5 pediatric deaths in foreign studies. These deaths occurred in patients on concomitant medications and complicated medical histories that contributed to the cause of death.

Data supported labeling for ages 2 years and above.

Relevant Labeling
Actemra® (tocilizumab)

1 INDICATIONS AND USAGE

1.2 Systemic Juvenile Idiopathic Arthritis (SJIA)
Actemra® (tocilizumab) is indicated for the treatment of active systemic juvenile idiopathic arthritis in patients 2 years of age and older**.**

2 DOSAGE AND ADMINISTRATION

2.2 Systemic Juvenile Idiopathic Arthritis (SJIA)

Patients less than 30 kg weight: 12 mg per kg every 2 weeks.
Patients more than 30 kg weight: 8 mg per kg every 2 weeks.

5 WARNINGS AND PRECAUTIONS

5.3 Laboratory Parameters: Systemic Juvenile Idiopathic Arthritis.

Changes in liver function tests, neutrophils, platelet and lipids are similar to those seem in adult rheumatoid arthritis patients.

Relevant Labeling, continued
Actemra® (tocilizumab)

8 USE IN SPECIFIC POPULATIONS

8.4 Pediatric Use

Safety and effectiveness of Actemra® in pediatric patients with conditions other than SJIA have not been established. Children under the age of two have not been studied. Testing of a murine analogue of tocilizumab did not exert toxicity in juvenile mice. In particular, there was no impairment of skeletal growth, immune function and sexual maturation.

12 CLINICAL PHARMACOLOGY

12.3 Pharmacokinetics

PK data provided for pediatric patients with Systemic Juvenile Idiopathic Arthritis (SJIA).

14 CLINICAL STUDIES

Study data in Systemic Juvenile Idiopathic Arthritis (SJIA) patients.

Actemra® Utilization in the U.S.
January 2010 Through June 2012, Cumulative

- Approximately 510,000 Actemra® vials were sold from manufacturer to retail* and non-retail** channels of distribution in the U.S.[1]
- Approximately 6,121 unique patients had a prescription or medical claim for Actemra® from a sample of 95 pharmacies and 1,400 clinics/hospitals/physician offices.[2]

Ages	0-1 years	2-17 years	18+ years
Patients with Rx or medical claims	2 (<1%)	118 (2%)	6,001 (98%)

*Retail channels include chain, independent, food store, mail order, and mass merchandise pharmacies in the entire United States.
**Non-Retail channels include hospitals, long-term care facilities, clinics, home healthcare providers, and HMOs in the entire United States.

1.Source: IMS Health, National Sales Perspectives™. January 2010 through June 2012. Data extracted November 2012.

2.Source: Source Healthcare Analytics ProMetis Lx. January 2010 through June 2012. Data extracted August 2012.

Actemra® Utilization in the U.S.
January 2010 Through June 2012, Cumulative

- Top Prescribing Specialties
  - 0-1 years: Pediatricians (100%)
  - 2-17 years: Pediatricians (67%), Rheumatologists (18%)
  - 18+ years: Rheumatologists (84%)

- Top Concurrent Diagnoses (~5,800 pts in sample)
  - 0-1 years: no diagnoses were reported
  - 2-17 years: “Juvenile Rheumatoid Arthritis NOS” (91.5%)
  - 18+ years: “Rheumatoid Arthritis” (99.6%)

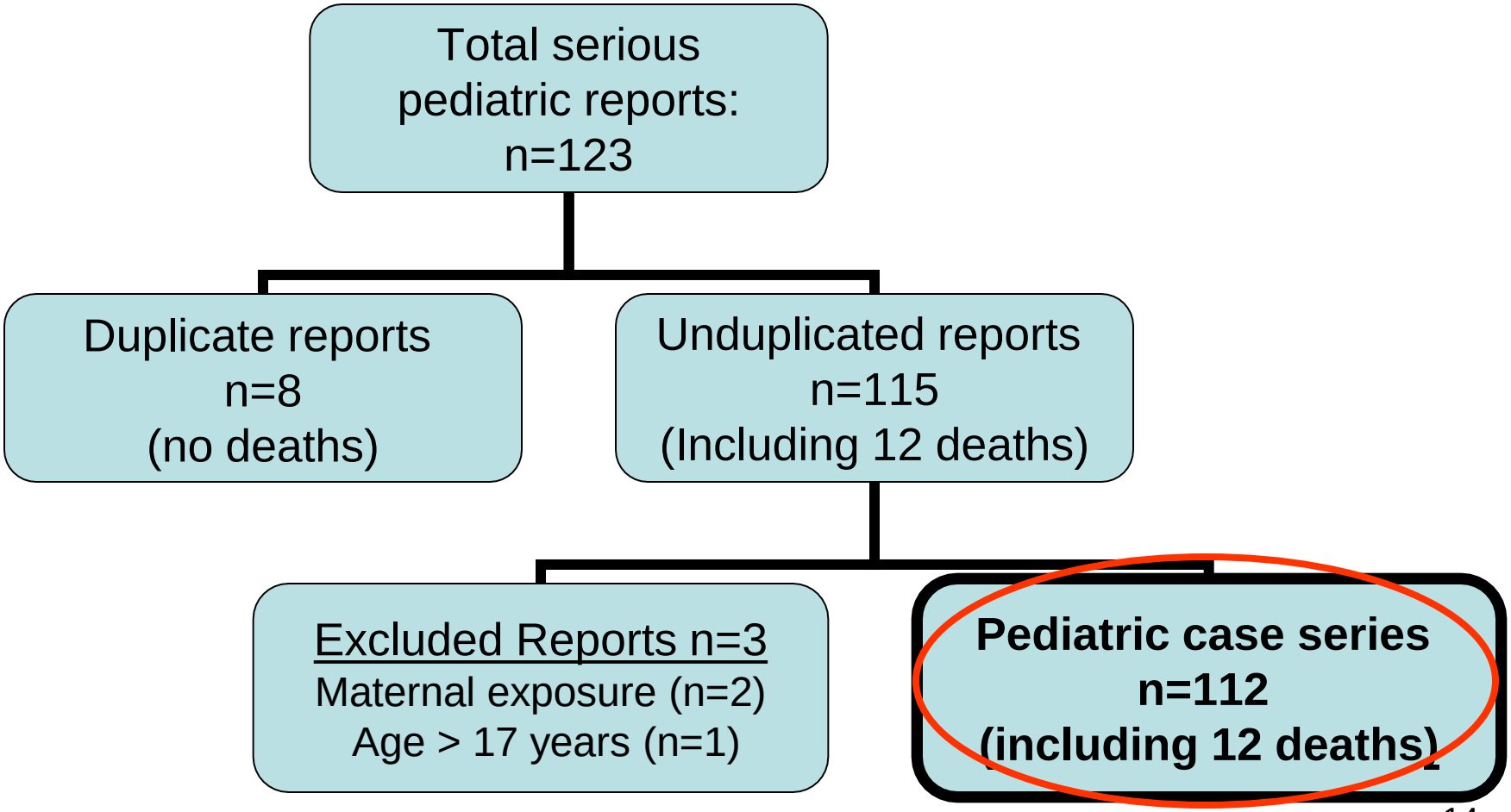
Source: Source Healthcare Analytics ProMetis Lx. January 2010 through June 2012. Data extracted August 2012.

Total Number* of Actemra® Adverse Event Reports (AERS) Since Approval (1/8/10 to 6/30/12)

	All reports (US)^	Serious (US)**	Deaths (US)
Adults (≥ 18 yrs.)	2376 (292)	2323 (268)	321 (34)
Pediatrics (0-17 yrs.)	118 (7)	115 (7)	7 (0)
Unknown Age ***	594 (112)	577 (107)	94 (35)#
All Ages	3088 (411)	3015 (382)	422 (69)

* May include duplicates and have not been assessed for causality.
^ US counts in parentheses.
**Serious adverse drug experiences per regulatory definition (CFR 314.80) include outcomes of death, life-threatening events, hospitalization (initial or prolonged), disability, congenital anomaly and other serious important medical events.
#Includes 5 deaths.

Pediatric Case Selection



Characteristics of Pediatric Cases Actemra® (tocilizumab) (n=112)

- Age (n=112)
  - Birth - 1 month (n=0)
  - 1 month - < 2 years (n=3)
  - 2 - 5 years (n=22)
  - 6 - 11 years (n=46)
  - 12 - 17 years (n=36)
  - Unknown (n=5)

- Primary Serious Outcomes (n=109)
  - Death (n=12)
  - Life-threatening (n=8)
  - Hospitalized (n=57)
  - Disability (n=1)
  - Other serious (n=31)

- Indications (n=112)
  - SJIA (n=79)
  - JIA/JRA (n=9)
  - PJIA (n=9)
  - RA (n=7)
  - Castleman's disease (n=3)
  - RAP (n=1)
  - Takayasu arthritis (n=1)
  - Unknown (n=3)

- Duration of Therapy (n=95)
  - Mean 7 months,
  - Median 4 months
  - Range 0 – 40 months

Definitions: JIA = juvenile idiopathic arthritis; JRA = juvenile rheumatoid arthritis; PJIA = polyarticular juvenile idiopathic arthritis; RA = rheumatoid arthritis; RAP = relapsing polychondritis; SJIA = systemic juvenile idiopathic arthritis

Deaths (n=12)
Actemra® (tocilizumab)

Macrophage Activation Syndrome (MAS) (n=3)

Multi-organ failure* (n=1)

Pulmonary hemorrhage* (n=1)

Respiratory Failure/hemorrhagic shock* (n=1)

Sepsis (n=1)

Cardiac arrest (n=1)

Acute respiratory obstruction (n=1)

Unknown (n=3)

Note: three additional cases were confounded by MAS.*

Macrophage Activation Syndrome*

- Known complication of SJIA and other rheumatic diseases.
- May be difficult to distinguish from disease flares or sepsis-like syndromes.
- Bone marrow shows macrophages with hemophagocytic activity.
- Patients may present with non-remitting high fever, hepatosplenomegally, encephalopathy and hemorrhage.
- 10% risk of overt MAS.
- 30–40% of SJIA patients may have subclinical MAS during disease flares.

* Ravelli, A et. al. “Macrophage activation syndrome as part of systemic juvenile idiopathic arthritis: diagnosis, genetics, pathophysiology and treatment.” Genes and Immunity (2012); 13; 289-298.

Macrophage Activation Syndrome, Continued

Main clinical, laboratory and pathological features of Macrophage Activation Syndrome	
Clinical features	**Laboratory features**
Non-remitting high fever	Cytopenia
Hepatomegaly	Abnormal liver function tests
Splenomegaly	Coagulopathy
Lymphadenopathy	Decreased erythrocyte sedimentation rate
Hemorrhages	Hypertriglyceridemia
Central nervous system dysfunction	Hyponatremia
	Hypoalbuminemia
	Hyperferritinemia
	Elevated sCD25 and sCD163
Histopathological features	
Macrophage hemophagocytosis in the bone marrow	
Increased CD163 staining of the bone marrow	

Deaths (n=12)
Actemra® (tocilizumab)

- **3 patients with SJIA in a clinical trial in Indonesia died of MAS.**
  - Patients were between 2 and 17 years of age. No other details were provided.
- **2 year-old with SJIA died of <u>multi-organ failure</u>.**
  - Developed MAS 3 months into treatment with tocilizumab and treated with dexamethasone, plasma exchange, and cyclosporine.
  - Later that month placed on IV antibiotics and ganciclovir for suspected infection.
  - Subsequently died of vasculitis, respiratory failure, and renal failure.

*Unlabeled events are underlined on this slide and subsequent slides.

Deaths (n=12), continued
Actemra® (tocilizumab)

- **7 year-old with SJIA died of pulmonary hemorrhage.**
  - History of MAS, disseminated intravascular coagulation (DIC) and hepatic failure.
  - Patient treated with steroid pulse therapy, plasma exchange for MAS. Tocilizumab was discontinued.
- **9 year-old died of respiratory failure and hemorrhagic shock.**
  - Patient had been on tocilizumab for SJIA for 3 years.
  - Developed MAS and pneumocystis pneumonia (PCP) and treated with antibiotics, pulse steroids, cyclosporine and plasmapheresis.
  - PCP progressed to hemopneumothorax and shock and patient died.

Deaths (n=12), continued
Actemra® (tocilizumab)

- **6 year-old with SJIA died of sepsis.**
  - On tocilizumab as part of a clinical trial for two weeks.
  - Concomitant medications were methotrexate and ibuprofen.
  - Developed gastroenteritis-type symptoms, taken to hospital, became unconscious and died.
- **16 year-old with SJIA died of cardiac arrest.**
  - History of right heart failure and pulmonary hypertension and pulmonary edema while using tocilizumab.
  - Tocilizumab was discontinued. Treated with steroids, antibiotics, diuretics and improved. Developed MAS and treated with cyclosporine.
  - Died one year after tocilizumab was discontinued.

Deaths (n=12), continued
Actemra® (tocilizumab)

- **13 year-old with Rheumatoid Arthritis died of <u>acute respiratory obstruction</u>.**
  - History included a tracheotomy, recurrent respiratory infections, and chronic bronchitis.
  - Presented to the Emergency Room with worsening of bronchospasm, urinary tract infection and tracheobronchitis and died the same day. Patient had been on tocilizumab for 6 months.

Deaths (n=12), continued
Actemra® (tocilizumab)

- **1 year-old with SJIA died of unknown cause.**
  - Premie with cleft palate and hypoplastic kidneys. Concomitant medications were methotrexate and ibuprofen.
  - Complicated medical history with interstitial pneumonia and “shock like state” just prior to death. Cause and timing of death not clear in the report. Event occurred sometime after the 13th dose of tocilizumab.
- **1 case of SJIA and 1 case of Still’s disease died of unknown cause.**
  - Age and medical history not reported in either case.

Serious Non-Fatal Adverse Events Actemra® (tocilizumab) (n=100)

Serious Infections (n=20)

Macrophage Activation Syndrome (n=13)

Hypersensitivity (n=11)

Gastrointestinal Events (n=10)

Hepatic Events (n=8)

Neurologic Events (n=8)

Malignancy (n=1)

Remaining Events (n=29)

Serious Non-Fatal Adverse Events, continued
Actemra® (tocilizumab)

Serious Infections: (n=20)

- Most patients (n=18) were on concomitant immunosuppressive agents.
- Eight patients reported multiple infections.
  - Infections included sepsis, gastroenteritis, pneumonia, bronchitis, herpes, abscess, infectious enterocolitis, cellulitis, mumps, otitis media, osteonecrosis, parvovirus, upper respiratory infection, pharyngitis and appendicitis.
- One case of latent tuberculosis.
- Actemra® has a boxed warning for serious infections, including tuberculosis.

*Unlabeled events are underlined on this slide and subsequent slides.

Serious Non-Fatal Adverse Events, continued
Actemra® (tocilizumab)

Macrophage Activation Syndrome (n=13):

- All patients had SJIA.
- MAS is associated with SJIA.

Hypersensitivity (n=11):

- Two cases of anaphylaxis and 3 more cases of possible anaphylaxis were reported.
- Symptoms reported were fever, angioedema, pruritus, rash, chest pain, cough, dizziness, hypotension, nausea, peripheral edema, shivering, and urticaria.
- Actemra® is labeled for hypersensitivity reactions, including anaphylaxis and death.

Serious Non-Fatal Adverse Events, continued
Actemra® (tocilizumab)

Gastrointestinal Events (n=10):

- Events included:
  - Enterocolitis (n=3)
  - Hemorrhage (n=3): Concomitant medications included corticosteroids, methotrexate (n=1) both labeled for GI bleeding.
  - Acute pancreatitis (n=1): patient was also on prednisone and cyclosporine, both labeled for pancreatitis.
  - Single cases of intussusception/pneumatosis, Ileus and gastric perforation.
- Warnings and Precautions section of labeling includes low platelets without bleeding.

Serious Non-Fatal Adverse Events, continued
Actemra® (tocilizumab)

Hepatic Events (n=8):

- Events included increased transaminases (n=5), hepatitis (n=2), and unspecified liver disorder.
  - Tocilizumab is labeled for increased transaminases.
- Cases of hepatitis:
  - 16 year old with SJIA and possible MAS developed hepatitis 20 months after initiating tocilizumab. Patient was also on methotrexate which is labeled for hepatotoxicity.
  - 8 year old with history of increased liver function tests developed hepatitis 2 weeks after starting tocilizumab. Patient was on multiple concomitant medications including methotrexate and acyclovir which is labeled for hepatitis.

Serious Non-Fatal Adverse Events, continued
Actemra® (tocilizumab)

Neurologic Events (n=8):

- Events included a single case each of cerebral hemorrhage, convulsion, demyelination, encephalitis, Guillain-Barre syndrome, pachymeningitis, pseudotumor cerebri, and reflex sympathetic dystrophy.
- Warnings and Precautions describes a theoretical risk of demyelinating disorders.

Malignancy (n=1):

- 16-year-old diagnosed with Stage II Hodgkin's lymphoma 2 months after receiving first dose of tocilizumab.
- Concomitant immunosuppressants included methotrexate and rilonacept (interleukin 1 inhibitor) for 18 months prior to initiation of tocilizumab.
- Warnings and Precautions describes a theoretical risk of malignancy.

Serious Non-Fatal Adverse Events, continued
Actemra® (tocilizumab)

Remaining Adverse Events (n=29):

- The most common events in this category included worsening or flares of rheumatologic disease (n=5) and nephrolithiasis (n=3).
- The rheumatologic events were considered related to the underlying indication for use.
- Nephrolithiasis is a labeled event based on studies of adult rheumatoid arthritis patients.
- The 21 remaining pediatric cases describe events that occurred only once. No safety signals were identified in these single cases.

Serious Non-Fatal Adverse Events, continued, Actemra® (tocilizumab)

Remaining Adverse Events (n=29)*	
Lymphopenia, splenic injury	Dysphagia
White blood cell count increased	Behcet's syndrome
Pericarditis	Systemic sclerosis
Arrhythmia	Spondylitis
Panniculitis	Radius fracture
Vasculitis	Abortion spontaneous
Rosaceiform dermatitis	Tic, scan abnormal
Acute febrile neutrophilic dermatitis	Nephrolithiasis, calculus urinary (n=3)
Pyoderma, erythema multiforme	Asthma, pericardial effusion
Papilloedema	Hypertension
Uveitis	Thrombosis
Disease progression, juvenile arthritis, arthritis, ill-defined disorder, fatigue (n=5)	
*Unless otherwise indicated, n=1	

Summary of Safety Reviews
Actemra® (tocilizumab)

- This concludes the pediatric focused safety review of AERS reports.
- Labeling includes approval in pediatric SJIA patients 2 years of age and older.
- The majority of adverse events were labeled (serious infection, MAS, hypersensitivity).
- The majority of unlabeled adverse events were associated with concomitant medications or underlying autoimmune disorders.
- No potential safety signals were identified.

Summary of Safety Reviews
Actemra® (tocilizumab)

- FDA recommends continued routine monitoring.
- Does the committee concur?

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