

Risedronate Sodium

Actonel[®], Actonel[®] with Calcium & Atelvia[®]
NDA #s 020835, 021823 & 022560

Warner Chilcott Co, LLC

Joint Meeting of the Advisory Committee for
Reproductive Health Drugs & the Drug Safety
and Risk Management Advisory Committee

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Warner Chilcott Representatives

Consultants

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Introduction

- ❑ **Warner Chilcott**
 - October 2009: acquired Procter & Gamble's global prescription pharmaceutical business, including the bisphosphonate, risedronate sodium
- ❑ **Risedronate Sodium**
 - ❑ **Actonel[®] (immediate-release tablet)**
 - 2000: approved for the treatment and prevention of postmenopausal osteoporosis
 - ❑ **Atelvia[®] (delayed-release tablet)**
 - 2010: approved for the treatment of postmenopausal osteoporosis; taken immediately following breakfast

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Risedronate Safety Database

Clinical Trials Experience in PMO

- ❑ 21,000 patients in over 20 clinical studies treated for up to 10 years, with the majority treated for up to 3 years
- ❑ 5-year placebo-controlled data
- ❑ Treatment discontinuation / interruption evaluated for 1 year following 2 years, 3 years and 7 years of continuous treatment

Post-Marketing Experience

- ❑ Risedronate-containing products approved in over 90 countries
 - Global alliance with sanofi-aventis
- ❑ Estimated patient exposure of ~27.7 million patient years including all indications

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Warner Chilcott Position on Risedronate Long-term Use and Drug Holiday (1)

1. Risedronate has established long-term anti-fracture efficacy at both vertebral and non-vertebral sites, including data from a 5-year placebo-controlled trial
2. Overall benefit-risk ratio for the long-term use of risedronate remains positive
 - No causal relationship to the use of risedronate has been established for ONJ, esophageal cancer, or atypical fracture

Sorensen OH, et al. Bone 2003;32(2):120-6.
Actonel Prescribing Information, February 2011. Available from: www.actonel.com/global/prescribing_information.pdf

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Warner Chilcott Position on Risedronate Long-term Use and Drug Holiday (2)

3. Insufficient data to support an *a priori* drug holiday at a specific time point and for a specific duration for all patients
 - The need for intermittent use and/or drug holiday may be evaluated on an individual patient basis by the physician and patient, taking into account risk factors, disease status, treatment history, and future treatment goals
4. FDA-approved labeling provides current and appropriate safety information and recommendations to physicians and patients, including the recommendation that physicians periodically re-evaluate the need for continued risedronate treatment

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Bisphosphonate “Drug Holidays”: Evolution of a Concept

1. Not a topic of discussion when BP 1st launched
2. Became a consideration after July 9, 2002 (WHI JAMA publication)
3. Better understanding of BP mechanism of action became available (Russell, Rogers, Ebetino, Nancollas et al)
4. FLEX study (Black D et al JAMA 2004) showed treatment with alendronate might be discontinued in some patients
5. FRAX™ became available to evaluate fracture risk
 - More to consider than just T-score alone
6. To date, not a standard of care in the USA

Miller PD. Best Pract Res Clin Endocrinol Metab 2008;22(5):849-68.

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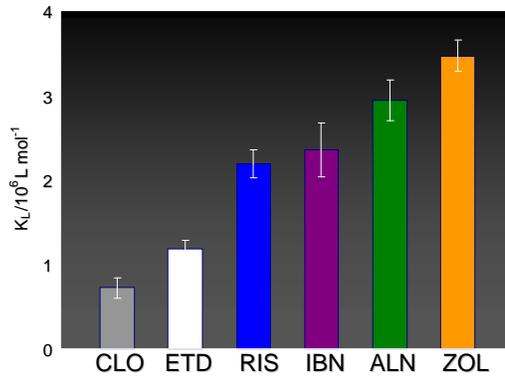
Efficacy and Safety Considerations Related to Interruption of Therapy (“Drug Holiday”)

- Do we know enough concerning the persistence or loss of effect upon interruption?
- Pharmacologic activity will persist because of drug reservoir in bone and re-cycling of BPs.
 - Activity will diminish to varying degrees over time.
- Pharmacological and biochemical differences exist among BPs in vitro and in vivo.

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Bisphosphonates Have Different Affinities for Hydroxyapatite (HAP)

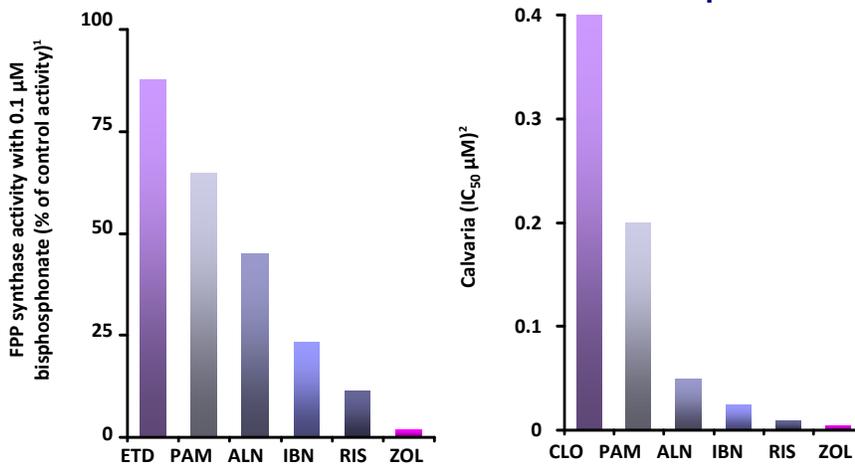
HAP Adsorption Affinity Constants at pH 7.4



Nancollas, Ebetino, Phipps, Russell et al, 2006. 38: 617-627

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Correlation Between Inhibition by BPs of FPPS and Calvarial Bone Resorption



ETD = etidronate; PAM = pamidronate; ALN = alendronate; IBN = ibandronate; RIS = risedronate; ZOL = zoledronate; CLO = clodronate

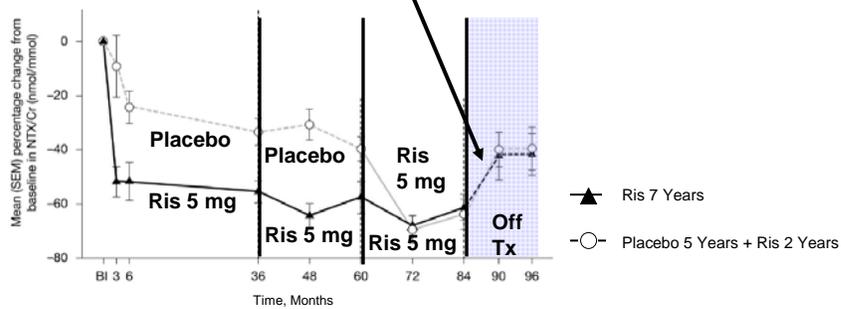
¹Dunford JE, et al. J Pharmacol Exp Ther 2001;296:235-42. ; ²Green JR, et al. J Bone Miner Res 1994;9:745-51. WC-10

Risedronate Long-Term Clinical Data

Effect of Risedronate Rapidly Reverses Even After 7 Years of Treatment

VERT-MN Study Extension (2001079)

During Year 8, no therapy was given and NTX levels rapidly increased in all patients, approaching levels seen during placebo treatment.



Continued Fracture Benefit with Continued Treatment Through 7 Years

VERT-MN Study Extension (2001079)

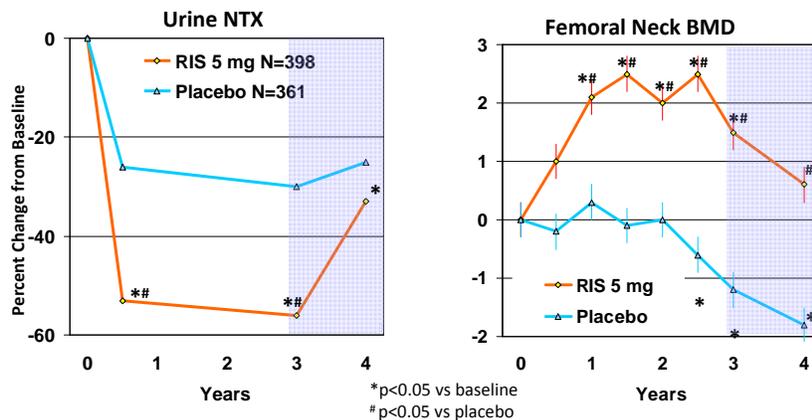
Percent of Patients with At Least One Osteoporotic Fracture
(morphometric vertebral and osteoporosis-related nonvertebral)
% (n Patients with Fractures / N Total Patients)

Treatment	Years 0 - 3	Years 4 - 5	Years 6 - 7
Ris 5 mg / Ris 5 mg / Ris 5 mg	19.3% (16/83)	15.7% (13/83)	12.0% (10/83)
Placebo / Placebo / Ris 5 mg	32.1% (26/81)	32.1% (26/81)	13.6% (11/81)

In Study VERT-MN, fracture rates continued to decrease in the patients treated with risedronate continuously for up to 7 years, suggesting continued fracture benefit with continued risedronate therapy.

Year 4 Off Therapy BTM & BMD Data

VERT-NA Study Extension (RVN008993)



During 1-year drug-free period after 3 years:

- BTMs (Urine NTX, BAP) returned to levels similar to the control group
- Lumbar spine and femoral neck BMD decreased

Year 4 Off Therapy Fracture Data VERT-NA Study Extension (RVN008993)

- In the North American registration (VERT-NA) study over 3 years, there was a statistically significant reduction in risk of vertebral and nonvertebral fractures for risedronate treated patients.
- In the patients taken off therapy and followed in year 4, the fracture benefit is no longer evident in former risedronate treated patients compared to former placebo treated patients.

Treatment During Years 0 to 3	Year 4 New Vertebral Fractures	Year 4 Non-vertebral Osteoporosis-Related Fractures
Placebo (N=361)	11.3%* (35/310)	3.6% (13/361)
Risedronate 5 mg daily (N=398)	9.4%* (31/331)	4.5% (18/398)

* Based on patients with known Month 36 radiographs and at least one post-treatment follow-up radiograph

Study RVN008993 Final Report, Nov 1999.

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Efficacy Endpoints and “Drug Holidays”

- BMD (primary) and BTM (secondary) are accepted as surrogate markers of fracture efficacy and registration for alternate dosing regimens.
- Interruption of risedronate therapy results in:
 - Rapid reversal of suppression of BTMs within 1 year, even after 7 years of treatment
 - Decline in BMD at some skeletal sites
- Continued risedronate therapy appears to provide continued fracture benefit.
- The data suggest that a fall in BMD and increase in BTMs are associated with a return of fracture risk soon after interrupting risedronate therapy.

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Conclusions

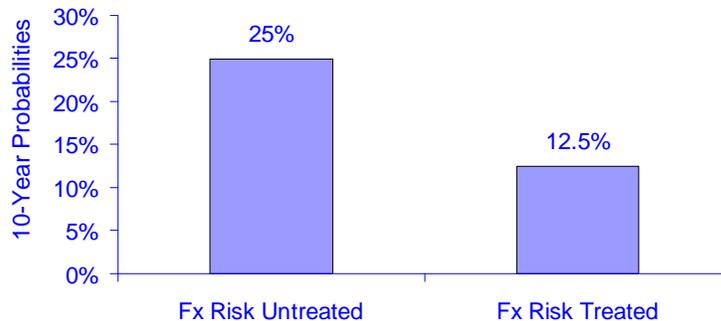
Conclusions (1)

BP “drug holidays” have become a hot topic due to:

- the special properties of BPs (not metabolized; re-cycled; some retention of biological effects after discontinuation)
- FRAX: validated 10-year risk data – more comprehensive assessment of fracture risk
 - There are patients who may have not needed therapy due to low risk
- Potential safety concerns with long-term use

Conclusions (2)

Overall benefit-risk ratio for the long-term use of bisphosphonates remains positive.

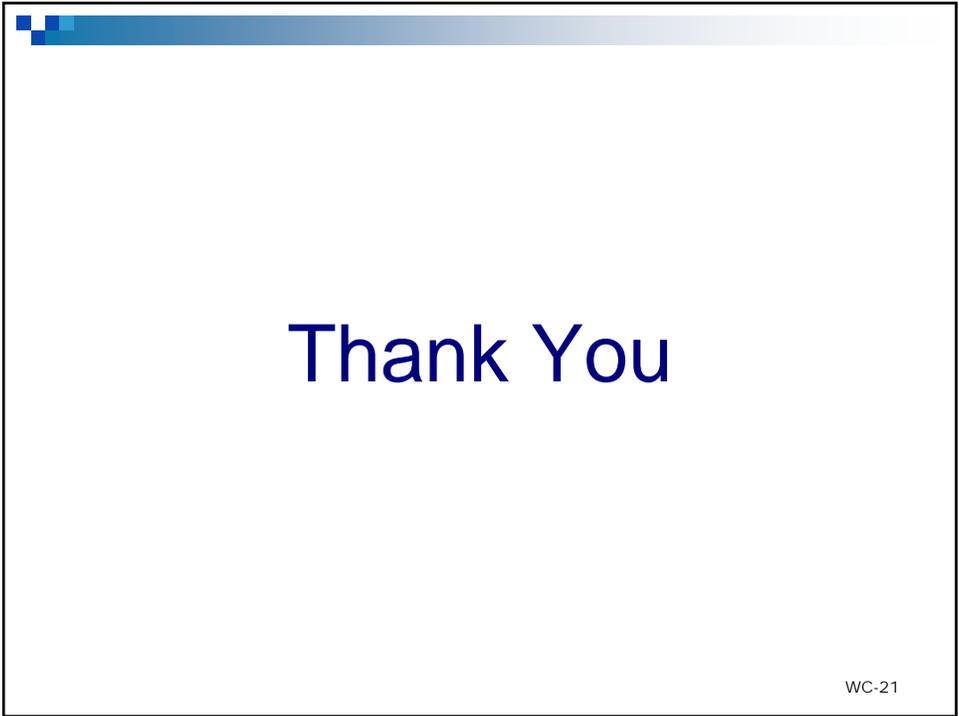


Untreated probability of major osteoporotic fracture calculated by FRAX based on 72-year-old woman with FN T-score of -3.0. Risk estimates assume long-term BP therapy resulting in 50% reduction in fracture risk. Image copyright © 2011 Lewiecki EM. Slide version. WC-19

Conclusions (3)

FDA-approved BP labeling provides current and appropriate information and recommendations to allow physicians to make informed treatment decisions for their patients

- Need to be very cautious in considering “drug holidays” in high-risk patients: prior fragility fracture; older with WHO osteoporosis @ hip or high fracture risk scores
- If drug therapy is interrupted, clinicians should consider monitoring BMD and BTM to assess loss of effect on turnover



Thank You