

1 very, very low; there's more important things for you
2 to deal with.

3 DR. TROENDLE: Dr. Marcus, you said that
4 half of the women would be above the median, but many
5 times when we're talking about bone density we're
6 talking about the mean for the pre-menopausal woman,
7 and the mean for this woman's age group may be
8 considerably lower --

9 DR. HIRSCH: They're osteoporosis or
10 something.

11 DR. MARCUS: Well no, actually, the T-score
12 and the Z-score at age 50 are pretty darn close. That
13 is, particularly of the spine. There is some loss at
14 the hip that's measurable across that couple of
15 decades before you hit age 50. But actually, mean
16 spine density at age 50 is maybe slightly lower, but
17 not so much so that a T-score and a Z-score are almost
18 exactly the same at that age.

19 I think that's pretty -- I'm going to ask
20 Ethel Siris to verify, and Mike McClung, but that's my
21 impression.

22 DR. SIRIS: I think that's generally true.
23 That I mean, if a woman has a positive T-score at age
24 50 you feel pretty good about her.

25 DR. MARCUS: Yes.

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1 DR. SIRIS: I mean, she's not likely to get
2 into a lot of trouble. If you sort of guess what she
3 might lose, she's not likely to get in a lot of
4 trouble. I think once you get into negative T-scores
5 you then have to make a judgment. A T-score of -1 at
6 50 isn't the same as a T-score of -1 at 63. So I
7 think if you got the measurement you can use that as
8 a piece of information.

9 ACTING CHAIR CRITCHLOW: Dr. Kreisberg.

10 DR. KREISBERG: Well, if the average life
11 expectancy of a woman is now close to 80 years,
12 average, then what is her average bone mineral density
13 going to be like? Are we going to have 80 to 90
14 percent of women surviving to the age of 80 having
15 osteoporosis?

16 DR. MARCUS: If you look at the frequency
17 distributions of bone mineral densities, in fact, by
18 World Health Organization criteria 50 percent of 80-
19 year-old women meeting that bone density criterion for
20 osteoporosis.

21 DR. HIRSCH: Fifty percent?

22 DR. MARCUS: Fifty. Five-zero percent. And
23 in fact, although I have problems with using a density
24 criterion as a gold standard for a porous bone,
25 nonetheless, the fracture incidence that you see in

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1 that group of people is pretty close to what -- you
2 know, it's not so far off. It's a realistic expecta-
3 tion of who really is going to fracture.

4 DR. HIRSCH: Really much higher than the 50
5 percent who have it than the 50 percent who don't have
6 it at that age?

7 DR. MARCUS: Yes, yes.

8 DR. HIRSCH: So I mean, what we're arguing
9 about is the incidence of the disease, or prevalence
10 of the difference ages, the severity. I mean, if
11 you'd got bitten by a dog there would be no question,
12 you'd get rabies vaccine with no talk, no FDA, no
13 fooling around.

14 So I mean, we're just talking about how much
15 of us -- how bad is it and who's going to get it. It
16 doesn't seem like we have very good predictors at the
17 moment of menopause. Isn't what we're sort of up
18 against? If we had good predictors there would be no
19 issue --

20 DR. MOLITCH: We do have good predictors.
21 We do have a bone mineral density that's a reasonably
22 good predictor and if you're at -1 then you in fact,
23 have very high risk for developing a fracture over the
24 next 20 years. If you have +1 at that point then you
25 have very low risk for a fracture in the next 20

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1 years. We do have a good predictor.

2 DR. MARCUS: Actually, if you look at the
3 percent increase in the effect of being fracture, for
4 every standard deviation change in bone density, as
5 Conrad Johnston and the National Osteoporosis Founda-
6 tion have pointed out on many occasions, this is a
7 more powerful index of risk than cholesterol for
8 myocardial infarction, or hypertension for a cerebro-
9 vascular accident.

10 DR. KREISBERG: It seems to me that if we're
11 going to permit physicians to make decisions to
12 prevent bone loss -- osteoporosis, Sol -- to prevent
13 osteoporosis --

14 (Laughter.)

15 -- to prevent osteoporosis and not every
16 physician has access to a bone densitometer, then
17 we're going to have to have a definition here that
18 allows some flexibility in making that decision.

19 And I wonder for instance, should all women
20 who are post menopausal, younger than 60 years of age,
21 and are at risk for developing osteoporosis, be
22 treated prophylactically? Or allow us to determine
23 low bone density on some empirical basis until we have
24 a marker or a measure of it that will be readily
25 accessible. I think that we need to in some way,

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1 figure out how we're going to give physicians the
2 opportunity of preventing osteoporosis.

3 ACTING CHAIR CRITCHLOW: Dr. New.

4 DR. NEW: How about this, Bob. Post-
5 menopausal women who are at risk for osteoporosis
6 should consider receiving alendronate. And I don't
7 think you should put an age, and I don't think that
8 you should say, should receive or should be adminis-
9 tered, but I think may consider is the way to put it;
10 which would allow the physician treating the patient
11 to make a decision.

12 I mean, the last thing we want is a recipe
13 for the treatment of menopausal women. What you want
14 is to have good medical judgment on it.

15 DR. HIRSCH: But you have to say there is a
16 powerful tool --

17 DR. NEW: Then I was going to add and say --

18 DR. HIRSCH: -- because I mean, along with
19 the risk factor and whatever. Like I've said, there
20 is a powerful tool -- we've heard that if they are at
21 +1 or -1 this is a very important predictor of what's
22 going to happen -- so I mean, you should also extend
23 it to say, women who are not on estrogen. So post-
24 menopausal, not on estrogens, are at hazard and here
25 are the risk factors or something. But I agree with

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1 you. It seems to me that some judgment has to be left
2 to the patient and the physician.

3 ACTING CHAIR CRITCHLOW: I mean, what is
4 your threshold going to be for a 55-year-old woman as
5 opposed to a 75- or 80-year-old woman? I mean, I know
6 we're probably talking here about under 60 because
7 that's what the trials were done in, but in practice
8 how would you approach the 55-year-old woman as
9 opposed to an 80-year-old?

10 DR. HIRSCH: I don't know. You could help
11 with that. I mean, I suppose if an 80-year-old woman
12 still had very high bone density you could say, well
13 let's forget about it. So I mean, that's somewhat
14 age-dependent also. But for a 45- or 50-year-old
15 woman that has it, that doesn't mean anything, unless
16 they are already beginning to show loss.

17 But otherwise, the younger you are the worse
18 this predictor is, in other words; the less likely it
19 is to be sensitive. Well it's certainly no good when
20 you're 20 years old. I mean, the extreme case. So at
21 some point this is --

22 DR. NEW: But she's not likely to be post-
23 menopausal.

24 DR. HIRSCH: Well I mean, at some age doing
25 a bone density just has no meaning. You know, just

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1 sort of a senseless thing to have done in respect of
2 all of this post-menopausal, etc., etc. So I don't
3 know at what age that occurs. At age 80 it also seems
4 like a meaningless endeavor.

5 DR. KREISBERG: It seems to me that we're
6 not -- we're talking about women across the entire age
7 span. For instance, the person who testified this
8 morning had a marked reduction in bone mineral density
9 and multiple fractures but was not pre-menopausal.

10 The idea here is this suddenly cuts in at
11 the age of 50 or 52 when women go through the meno-
12 pause. It seems to me that physicians would like the
13 option of having identified a younger, pre-menopausal
14 woman who has marked reduction in bone density as
15 being a candidate for this drug.

16 DR. HIRSCH: But we're all set with that.
17 We've got a drug and that's approved, she can take it
18 --

19 DR. KREISBERG: That's right.

20 DR. HIRSCH: -- that's not what we're
21 talking about. We're talking about the person who
22 isn't -- that we're trying to prevent something, and
23 who doesn't have the -- and I guess the issue of the
24 bone density is to try to get the subtle issue across
25 of when this is important to measure and what it means

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1 at different ages.

2 DR. KREISBERG: Well, we have always made
3 recommendations -- population recommendations to
4 prevent disease. That's what the cholesterol-lowering
5 diet is all about, even though there are some people
6 who will benefit and other people who follow the diet
7 that will not benefit.

8 It seems to me that it's more important to
9 prevent the disease than it is to treat the disease
10 once it becomes either clinically or densitometry --
11 well, by bone densitometry, obvious.

12 As a result of that, I think that these
13 types of decisions are, by the nature of them, going
14 to result in the treatment of patients who will not
15 benefit in order to find and treat the patients who
16 will benefit, until we have better techniques to be
17 able to segregate them differently.

18 And therefore I think, all women at the time
19 of menopause, are either candidates -- all women are
20 candidates at one time or another, to receive this to
21 prevent bone mineral loss.

22 DR. HIRSCH: I agree, and the downside is
23 what it costs or you know, otherwise -- and that after
24 40 years everyone taking this may get osteogenic
25 sarcosi. You have no idea; we don't know. So I mean,

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1 there's always a downside, otherwise you would just
2 put it in the drinking water. Free and fine, we'd all
3 take it.

4 ACTING CHAIR CRITCHLOW: Dr. Goldmann.

5 DR. GOLDMANN: Taking up, Dr. Critchlow,
6 your suggestion, I thought it might be helpful to
7 actually show our indication, because what we tried to
8 do and as we discussed, was to indicate it for women
9 at risk.

10 So in that indication we said -- and using
11 Dr. New's language -- for the prevention of osteoporo-
12 sis, Fosamax™ should be considered in post-menopausal
13 women who are at risk of developing osteoporosis, and
14 for whom the desired clinical outcome is to maintain
15 bone mass and reduce the risk of future fractures.

16 We then go on to try to identify the
17 patients. Bone loss is particularly rapid in post-
18 menopausal women younger than age 60. Risk factors
19 often associated with the development of post-meno-
20 pausal osteoporosis include, but are not limited to:
21 early menopause, moderately low bone mass, thin body
22 build, Caucasian or Asian race, and family history of
23 osteoporosis.

24 The presence of such risk factors may be of
25 value when considering the use of Fosamax™ for

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1 prevention of osteoporosis.

2 So that was our intent, to keep the wording
3 to give -- we can't create medical guidelines in a
4 label, but the idea was to take the state-of-the-art
5 as it exists to help identify those patients who are
6 considered at risk.

7 DR. NEW: Would you consider putting the
8 phrase in, women who are not being treated hormonally?

9 DR. GOLDMANN: The issue about estrogen
10 replacement is a very interesting one. It's not our
11 intent that if someone is successfully being managed
12 with HRT they should be continued on HRT and we're not
13 saying that you should be using alendronate. It's a
14 question again, of choice and not proscribing someone
15 or saying that you should be using one rather than the
16 other.

17 And I think that as a physician, speaking
18 for myself, if I were faced with a patient, I would be
19 talking to the patient about options. I would talk to
20 them about HRT, the advantages and disadvantages; I
21 might talk to them about alendronate.

22 For a woman obviously, who has other issues
23 -- symptoms of menopause, heart disease, or family
24 history -- obviously HRT may be a better choice. For
25 a women who doesn't want to take it or has, you know,

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1 reasons not to take an HRT kind of preparation,
2 alendronate would be a better choice.

3 But I think it's got to be a question of
4 choices, just like that. You can't -- I would be
5 loathe to have the physician being told, you have to
6 try this or you have to try that.

7 DR. NEW: Well you remember earlier I asked
8 whether it was an either/or proposition, and I never
9 got a clear answer. In other words, if you give the
10 person the option --

11 DR. GOLDMANN: It is an either/or but again
12 -- and we have other things in our label -- but it is
13 an either/or. When a patient comes to you and asks,
14 or says they're interested in treatment, a reasonable
15 physician -- when you're faced with a hypertensive you
16 don't just say, there's only one drug for you. There
17 may be reasons you'd want to use a calcium channel
18 blocker or some other drug. There are different
19 classes of drugs. This is an option that's available
20 to a women.

21 DR. HIRSCH: But it's a centrally important
22 -- I agree with Dr. New in a way it ought to be in the
23 first sentence for those post-menopausal women who are
24 not receiving estrogen replacement. Then I think it
25 reads wonderfully well. But it seems to me leaving

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1 that out is leaving out a central --

2 DR. GOLDMANN: That's actually in another
3 part of the label, but we are not at a point -- we
4 haven't finished any studies -- we are not recommend-
5 ing that women who are being managed successfully with
6 HRT should be either switched or put onto alendronate.
7 So if that's what your intent is, and there is a part
8 actually -- I believe it's in the clinical pharmacolo-
9 gy section -- that discusses the fact that we haven't
10 used the drugs together, etc. There's a study
11 ongoing. So --

12 DR. NEW: But the estrogen treatment is more
13 effective if -- this is table 7 that shows the
14 estrogen/progestin treatment is more effective on
15 lumbar spine measurements.

16 DR. GOLDMANN: Yes, there's a difference,
17 Dr. New. You weren't here for the presentation.
18 There are two different stratum that we use for
19 estrogen. The first stratum, one stratum, was
20 European cohort. In that stratum the drug that was
21 used is not available in the United States and
22 actually has independent -- besides its estrogen
23 effects -- it has androgenic effects as well.

24 That's what you're looking at. It's less
25 clear in the preparations, although clearly, estrogen

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1 did show it was better -- that is true. It's not
2 quite as dramatic.

3 DR. MOLITCH: I think I can certainly live
4 with the way things were up here on the indications,
5 and I think we have to educate physicians and every-
6 thing, in how to use this one versus another therapy.

7 What concerns me a little bit down the road
8 a little bit is what one of our spontaneous speakers
9 said this morning before we started -- was the ads
10 that get into the lay publications is where I have a
11 little bit more concern within those kinds of ads.

12 I know the FDA has some control over this
13 later on about the balance of estrogen versus alendro-
14 nate under those circumstances, and I think that's
15 where I would have more of a concern. I think -- here
16 I think I don't really have any problem with this.

17 DR. TROENDLE: Dr. Critchlow, the question
18 2b which we've been considering, deals with low bone
19 density in women who are not yet osteoporotic by
20 definition. "C" deals with risk factors by them-
21 selves. It says, instead of bone density measurement.

22 It seems to me that what I'm hearing is that
23 everybody wants everyone to have low bone density if
24 it's available. Maybe we should sort this out so that
25 we're dealing with one group of women to whom it's not

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1 available, and say how we should identify it in that
2 group, and another could be just based on the measure-
3 ment of density. Would that help?

4 DR. HIRSCH: I thought what we heard is when
5 that's available it's a pretty powerful tool to
6 establish risk. But it's not absolutely the only
7 necessary way of deciding whether or not to use this.

8 DR. TROENDLE: Even when it's available
9 you're saying there are other factors to be consid-
10 ered? So you want both bone density and the other
11 risk factors?

12 DR. KREISBERG: Well, I think the decision
13 to get a bone density is frequently based upon the
14 other risk factors. The bone density is probably the
15 single most compelling reason to use an anti-osteopo-
16 rosis regimen and to make the decision to intervene.

17 It seems to me that if we're talking about
18 how to word this, is that ideally, decisions should be
19 based on bone mineral density measurements, but there
20 may be circumstances in which bone mineral density
21 measurements are not available, and then risk factors
22 and clinical judgment should be used by the physician
23 in making the decision to use the drug.

24 DR. MARCUS: I think that one could look at
25 what the National Cholesterol Education Project had to

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1 deal with when they made guidelines for LDL levels to
2 be optimally at 130 or below, and so forth.

3 Recognizing that this had to be done based
4 on LRC standardized laboratories and that those
5 laboratories were few and far between, there was
6 nothing stated in literature about what the person
7 should do who lives in a community where there is no
8 LRC standardized laboratory.

9 I don't know why we have to be, in a similar
10 sense, responsible for dealing with the problem of
11 access. I think we should define what we think are
12 the best criteria for a selection of patients and
13 monitoring them, and then the problem of access really
14 has to be dealt with on a national level with agencies
15 such as HCFA and Medicare, etc., etc.

16 I don't see that that's our role to try to
17 come up with something which is clearly second-best to
18 satisfy that problem.

19 ACTING CHAIR CRITCHLOW: I don't think we're
20 in a position to compare the predicted value or
21 probability of osteoporosis in those various situa-
22 tions.

23 DR. TROENDLE: Are you saying that the label
24 could say that the decision should be based on bone
25 density even though we know that it's not going to be

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1 possible for everyone to get bone density?

2 DR. HIRSCH: See, even in those programs
3 they waffled a lot in -- for example, the National
4 Cholesterol Education Program decided that a total
5 cholesterol originally of 200 milligrams percent was
6 going to be a dividing line. If you're above that do
7 something and if not -- now then, the American Heart
8 Association didn't do that. They said no, no, the
9 whole country should change its diet, but then there
10 are other restrictions, other things that you do at
11 different levels.

12 So we're sort of in the same fix here in a
13 way because if you tell me that 50 percent of women at
14 age 80 are going to be at higher risk for fractures
15 because of osteopenia or whatever, there's something
16 that you can do to prevent it -- well, you can almost
17 sort of make the case of saying yes -- you're getting
18 close to the point of saying everyone who is not on
19 estrogens ought to be on this stuff.

20 On the other hand, that may be too extreme
21 a thing, in which case you want to establish some
22 levels of hazards. And we're at that stage almost, of
23 deciding, what are the different things. Now, you say
24 that the --

25 ACTING CHAIR CRITCHLOW: I don't think we

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1 can do that here though.

2 DR. HIRSCH: I don't see how we can,
3 although it's clear that there are some things that
4 are very good predictors.

5 ACTING CHAIR CRITCHLOW: Dr. Molitch.

6 DR. HIRSCH: The numbers are big when it's
7 50 percent of the limit.

8 DR. MOLITCH: I'll ask Dr. Kreisberg if he
9 would put everybody on a pharmacologic cholesterol-
10 lowering agent -- since that's what you're essentially
11 proposing here -- as opposed to encouraging everybody
12 to exercise and to have adequate amounts of calcium in
13 their diet, which would be equivalent to lowering the
14 cholesterol in their diet and exercising.

15 Now it's in another stage where you're going
16 to pharmacological therapy other than estrogen
17 replacement. So that we could make the same argument
18 to take everybody in the country at a certain age and
19 put them on a pharmacologic cholesterol-lowering
20 agent. Are we willing to do that?

21 DR. KREISBERG: Well, I think there's a
22 difference. I don't happen to believe that the
23 studies demonstrate that exercise makes a difference
24 in bone mineral density. But obviously we would all
25 agree that calcium intake should be optimized and

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1 vitamin B status should be clarified and optimized.

2 But the problem here is that almost every
3 woman who ages is likely to develop osteoporosis, and
4 50 percent of them will have fractures. And so it
5 seems to me that this is almost like a population-
6 based recommendation rather than a targeted recommen-
7 dation.

8 And that does get back to cholesterol. I
9 mean, if you make population-based recommendations it
10 probably doesn't benefit many patients within the
11 population, but the population's mean average moves
12 lower. And if you do it targeted then you can
13 identify patients who are likely to derive much
14 greater benefit from the manipulation.

15 But measuring cholesterol, even though it's
16 not standardized with the LRC, is actually pretty easy
17 to do, but getting a bone mineral density isn't. And
18 I think that physicians have to be given the opportu-
19 nity of making empiric decisions.

20 ACTING CHAIR CRITCHLOW: Wouldn't they do
21 that whether or not bone mineral density was avail-
22 able? Wouldn't they make some sort of decision as to
23 whether or not --

24 DR. KREISBERG: Well, they probably would
25 but it would be nice to say that that is one way of

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1 making a decision.

2 ACTING CHAIR CRITCHLOW: Given the number of
3 questions that we have to consider we can go one of
4 two ways. We can certainly proceed with the rest of
5 the discussion, but would the committee feel comfort-
6 able in voting on the first two questions now, or
7 should we finish discussing the remaining questions
8 and vote at the end?

9 DR. KREISBERG: You're the boss.

10 ACTING CHAIR CRITCHLOW: Does anyone feel
11 the need of a break or -- either way. Shall we resume
12 discussion or would people -- okay.

13 Question 3, just revisiting the 2.5 versus
14 five milligram recommendation. Has that been dis-
15 cussed to everyone's satisfaction, or are there some
16 further comments or questions on that?

17 DR. KREISBERG: I have a question for the
18 Agency. I mean, are they going to be open to a dose
19 ranging type of recommendation, or for the purposes of
20 simplicity, do they want a single dose?

21 DR. TROENDLE: Well, I guess that so far as
22 I can see, a choice of doses might be better because
23 the data are based on a variety of people.

24 ACTING CHAIR CRITCHLOW: Comments on that?
25 Dr. Illingworth.

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1 DR. ILLINGWORTH: Given the lack of avail-
2 ability of bone density measurements to potentially
3 use the drug, if we're going to use lack of response
4 to 2.5 milligrams in a given patient based on subse-
5 quent bone density measurements, it's going to put a
6 lot of patients through repetitive bone density
7 measurements.

8 Given the data we've heard this morning,
9 that a quarter of patients on 2.5 milligrams per day
10 did lose bone, and only 14 percent on five milligrams
11 per day did, my personal view would be to say, if
12 you're going to treat patients, treat them with a dose
13 that we know is more effective, and hence, use the
14 five milligram dose as the recommended starting dose.

15 ACTING CHAIR CRITCHLOW: Yes?

16 DR. TROENDLE: I think I've heard from
17 people like Dr. Marcus and others that they'd like to
18 have available a two-and-a-half milligram dose so that
19 they can make that decision at the time they saw the
20 patient, and maybe based on a number of things at that
21 time.

22 ACTING CHAIR CRITCHLOW: But -- please.

23 DR. ROSENBLATT: I wonder if I can make a
24 comment. My name is Dr. Michael Rosenblatt and I'm a
25 professor of medicine at Harvard Medical School. And

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1 one subject that we've not talked about is the
2 temporal play over which bone loss and osteoporosis
3 occurs. And so the physician having to prescribe as
4 I do in my office when a woman comes to see me, has to
5 decide about starting the patient on a particular
6 dose.

7 There's a point I would like to emphasize
8 and that is, that the first year or two of therapy
9 gives us a different opportunity than the subsequent
10 years. Women lose about a third of the bone loss that
11 they will lose over their entire lifespan, in the
12 first six years after menopause.

13 So for me, it's pretty clear that when that
14 patient comes in, those first couple of years are much
15 more critical and an opportunity that I can't revisit.
16 So knowing that the five milligram dose is more
17 effective, I think that I wouldn't take the chance of
18 starting at a lower dose and then ratcheting up. I'd
19 much rather start -- and we're talking about large
20 populations, what dose you start at.

21 So I just want to emphasize that there's a
22 temporal play here and that the first couple of years
23 are much more important than the subsequent years.

24 ACTING CHAIR CRITCHLOW: Does anyone have
25 concerns as to the degree or effect -- magnitude of

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1 the effect of the two-and-a-half gram dose in actual
2 clinical practice? I mean, my guess would be that
3 what we see in a clinical trial setting is a best-case
4 scenario. If there are other comments on that?

5 DR. KREISBERG: Well, I don't understand why
6 you couldn't say that the generally recommended dose
7 is five milligrams, and that if you have access to
8 bone densitometry that you might consider as little as
9 2.5 or as much as ten.

10 DR. MOLITCH: I think, you know, five
11 milligrams seems like a very reasonable dose to
12 recommend -- especially since we're not doing bone
13 mineral densities it sounds like -- and that it will
14 be left to people like Dr. Marcus and others who have
15 a lot of experience with this that may want to alter
16 doses and give different doses. But I think as a
17 general recommendation, five seems like a very
18 reasonable thing.

19 DR. MARCUS: May I ask if the company plans
20 to develop this as a scored tablet at five milligrams?
21 It's a stability issue. So if you do a two-and-a-half
22 milligrams it has to be a separate pill, okay.

23 DR. MOLITCH: Or every other day.

24 DR. MARCUS: Well, every other day on a
25 medication like this is really tough, I think.

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1 DR. KREISBERG: You can cut it, even if it's
2 not scored.

3 DR. NEW: Yes.

4 ACTING CHAIR CRITCHLOW: Dr. Sobel.

5 DR. SOBEL: Yes, I just wanted -- perhaps
6 the company could clarify or fortify its position, as
7 the recommendation stands now for prevention, the
8 recommended dosages, five milligrams once a day. Now,
9 in support of that I just want you to -- perhaps if we
10 could, if you amplified on the reasons for that
11 selection and your desire to adhere to that, just as
12 -- yes.

13 DR. YATES: I think what we're facing with
14 osteoporosis is very different to hypertension,
15 cholesterol, or replacement of thyroid hormone in that
16 in each of those we have the opportunity to bring the
17 patient back in a month or two and look at a test or
18 evaluate the patient's blood pressure, and then make
19 dose adjustments.

20 We believe that we have to select an
21 appropriate dose, the appropriate dose, for prevention
22 of osteoporosis in this population. And the arguments
23 have already been made at various sites -- the spine,
24 the total body, and the hip -- that there is a higher
25 proportion of patients losing bone -- including just

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1 over 50 percent of patients at the total body with the
2 2.5 milligram dose -- the losses or the proportions of
3 patients with loss at the five milligram dose is
4 consistently in the order of 10 to 20 percent smaller
5 than the proportions of patients losing bone at the
6 2.5 milligram dose.

7 And the problem is exacerbated in the real
8 world beyond that that we see in our clinical trial
9 environment in that, often patients are being measured
10 on different densitometers at different points in
11 time. So it's not really possible to titrate patients
12 now or actually in the near, foreseeable future, to
13 evaluate the efficacy.

14 Our real concern is that we're going to be
15 undertreating a significant proportion of women and as
16 Dr. Rosenblatt indicated, that these women are going
17 to be losing bone at a time when we know -- particu-
18 larly early post-menopausally -- that they're having
19 a very substantial decrease in their bone mass and
20 loss of normal architecture.

21 So given the very good safety experience as
22 well, we feel very comfortable that the risk/benefit
23 relationship actually dramatically favors the five
24 milligram dose over 2.5.

25 And the final point is as was discussed

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1 earlier on today, estrogen is the standard therapy for
2 current prevention of osteoporosis. Five milligrams
3 does produce effects which are close to those that
4 we've seen with standard doses of Premarin and Provera
5 -- the 2.5 milligrams is less effective than that. So
6 that's another argument that can be brought into the
7 mix that helps us to feel that five milligrams is
8 clearly the correct dose.

9 DR. SOBEL: Another question is, occasional-
10 ly we assign to drugs in the labeling, first and
11 second line status. Do you have any feeling for that?
12 I mean, there's an appreciably good case to be made
13 for estrogen as being first line therapy and alendron-
14 ate second line. Do you feel that some amplification
15 of this idea should occur in the labeling?

16 DR. YATES: I truly believe that it should
17 not and the reason is that, clearly, arguments have
18 been made very coherently today that estrogen is a
19 very good treatment for women where the benefits are
20 there and tolerability is good and the concerns about
21 risks are low.

22 But that does not involve all women. There
23 are a large number of women who cannot tolerate
24 estrogen or have a contraindication. And so what we
25 have to do is to weigh a bone-specific treatment on

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1 the one hand -- alendronate -- against a treatment
2 which is actually much broader than that -- estrogen
3 on the other -- in terms of their overall
4 risk/benefits for individual patients.

5 And it would be not consistent with the
6 practice of medicine to dictate that women should,
7 maybe against their will, try to go on to a hormonal
8 regimen, if in fact that, in their own estimation and
9 their physician's estimation, is something that they
10 choose not to do, and if they choose instead to take
11 something which is a more specific therapy for
12 prevention of bone loss.

13 ACTING CHAIR CRITCHLOW: But don't you think
14 in actual practice -- well, I don't know -- would
15 women choose to go on estrogen first, or wouldn't
16 physicians feel more comfortable in prescribing that
17 first?

18 DR. YATES: I'm sure Dr. Siris can probably
19 answer that question better than I.

20 DR. SIRIS: I think most physicians,
21 hopefully, would take the position of offering a
22 series of options. Because the reality of it is that
23 a great many women don't want estrogen, even when it's
24 offered to them and they're given all of the positiv-
25 es. They are concerned about some of the negatives.

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1 And I would certainly hope that we would not
2 put physicians into this situation where they would be
3 required to give a course of estrogen before being
4 permitted to try alendronate. If a woman demanded
5 alendronate and the doctor decided that was the most
6 logical thing for her and she was given it instead of
7 estrogen, in theory that physician was not following
8 the regulation which said that it's second-line
9 therapy.

10 I think we have to consider these are
11 relatively equivalent for the purpose of preventing
12 the loss of bone and that given these data, physicians
13 and patients should discuss the pros and cons of each
14 and make decisions that are individualized for the
15 patient who's sitting across the table from the
16 physician. I mean, I would think most physicians
17 would be comfortable with that.

18 ACTING CHAIR CRITCHLOW: Dr. Colley.

19 DR. COLLEY: I guess I would agree with the
20 suggest of Dr. Sobel that in promotional materials or
21 advertisement that treatment with alendronate be
22 placed in some context with estrogen. When patients
23 read about new things there's an assumption sometimes
24 that new is better.

25 They may come to their physician with an

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1 impression that this is what they have in their mind
2 that they want, and they should be better educated
3 before they get there -- before they are set on a
4 particular therapy.

5 DR. HIRSCH: I agree with that. I think
6 it's a very strong piece of information that everyone
7 should be given. Namely, this is a drug for post-
8 menopausal women not receiving estrogen. That just
9 ought to be said right-out. I mean, I agree that
10 there ought to be the discussion of you should be on
11 it or not, but that's another matter. I mean, what
12 this drug is for, the indication of this drug is for
13 that specific -- I would feel very strongly that ought
14 to be right up-front.

15 ACTING CHAIR CRITCHLOW: Is the committee
16 agreed on that?

17 DR. KREISBERG: Agreed on what? That
18 alendronate should be considered by women who are
19 unable or unwilling to take --

20 ACTING CHAIR CRITCHLOW: Or not receiving --

21 DR. HIRSCH: No, no.

22 ACTING CHAIR CRITCHLOW: Not receiving
23 estrogen.

24 DR. HIRSCH: This is for post-menopausal
25 women not receiving estrogen -- not unable or unwill-

1 ing or anything else. I mean, that's the whole issue.
2 We don't want to get involved in whether they're
3 unable to unwilling, but just to say what this drug is
4 for. It's for the reduction of loss of bone mass
5 after the menopause in those who are not receiving
6 replacement therapy with estrogen. Period.

7 DR. KREISBERG: Who are not receiving.

8 DR. MOLITCH: We can't do that because it
9 may be indicated, or we may feel that it can be used
10 in addition. We don't want to shoot ourselves in the
11 foot at this point.

12 DR. HIRSCH: Well it isn't. I mean, that's
13 the whole point. I --

14 DR. MOLITCH: No, no, no, that's not. As
15 Dr. Marcus said before, there are clearly women who
16 are on estrogen replacement who are going to continue
17 to fracture. We may want to add alendronate to those
18 women. So you don't want to shoot yourself in the
19 foot by doing the kind of labeling you just proposed.

20 ACTING CHAIR CRITCHLOW: Although we have no
21 data in front of us to evaluate that.

22 DR. MOLITCH: Well, there may be data that's
23 forthcoming, we understand. At least -- but don't --
24 I mean, we don't want to preclude ourselves from what
25 may be helpful. I mean, you're saying you can't use

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1 it.

2 DR. HIRSCH: Well, I wouldn't say you can't
3 use it but I would say what it's for.

4 ACTING CHAIR CRITCHLOW: Unfortunately, the
5 studies that would be cited in the label would be
6 among those women who are not receiving estrogen.

7 DR. HIRSCH: I just think this notion ought
8 to be up front with this -- in the -- I'm not sure I
9 can think of the most concise wording of it this way,
10 but somehow this ought to be up-front and not just
11 buried somewhere deep in the message -- for the very
12 reasons brought up.

13 Because this is going to appear in newspa-
14 pers as the great new thing or something. This ought
15 to be made evident right away because 30 percent, 40
16 percent or whatever, are on estrogen and you don't
17 want them to --

18 DR. MARCUS: Could you change the wording
19 just slightly to say that it should be considered by
20 women who are not receiving adequate replacement doses
21 of estrogen.

22 DR. HIRSCH: Well, I don't know what that
23 means.

24 DR. MARCUS: Well, that just leaves a window
25 for the woman who is having fractures or is continuing

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1 to lose bone despite being on hormone replacement.

2 ACTING CHAIR CRITCHLOW: Dr. Goldmann.

3 DR. GOLDMANN: A couple of things. First of
4 all, as I stated we do have it in the label -- and
5 maybe we have to strengthen it -- but we do have
6 wording about estrogen and alendronate and that you
7 don't use them together.

8 It's sort of interesting listening to this.
9 When you have therapeutic options in most areas, you
10 don't usually write out other people's drugs in your
11 therapeutic options. And I think there has to be some
12 balance. As I said, we are not suggesting that people
13 should either stop HRT if they're on it, or not use it
14 if it's the right drug for them. We're simply talking
15 about options.

16 To get to one other point when Dr. Sobel
17 brought up, you know, first line versus second --
18 something that Dr. Marcus has talked about. If you
19 put in something that clearly makes this look second
20 line, women who choose to use it who don't want to
21 take estrogen, may not get reimbursed.

22 So there are real implications in today's
23 world and I don't think the data really supports that.
24 I think that we are talking about individual patients
25 who need options to discuss it with their physicians,

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1 and I don't think we should put physicians in a
2 position where they have to do something that they
3 don't think is right for the patient.

4 ACTING CHAIR CRITCHLOW: I mean, am I
5 correct in the label that discussion of estrogen
6 occurs in the precautions, or contraindications, or
7 safety section? I'm not sure that specifically
8 addresses these concerns.

9 DR. NEW: May I just, while we're waiting
10 say, how can we decide whether estrogen should be
11 added or alendronate should be added since we haven't
12 seen any data on the combination?

13 ACTING CHAIR CRITCHLOW: Any other comments
14 on that issue? I don't know what the --

15 DR. KREISBERG: We are going to vote on this
16 one, aren't we?

17 ACTING CHAIR CRITCHLOW: We're going to vote
18 on it. Any concerns, comments, or issues with the
19 safety benefit versus risk?

20 DR. NEW: Could I have an explanation? Dr.
21 Goldmann said that if we say that this is recommended
22 -- or the indication for its use is in women not
23 receiving estrogens -- is there very good evidence
24 that under those circumstances insurance policies will
25 not reimburse somebody who isn't -- I don't know about

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1 this. I really need to know.

2 DR. GOLDMANN: I'm not sure with that
3 wording that that would be a problem. We'd have to
4 look at --

5 DR. NEW: I don't think so.

6 DR. GOLDMANN: No, but if you clearly start
7 making distinctions as if you have to have been
8 receiving estrogen or a trial of estrogen should be
9 first or any of that. But something like not receiv-
10 ing, which is consistent with the precautionary
11 information we have, and it's consistent with our
12 philosophy. We do not have data that would recommend
13 someone being on both. We don't have the data at
14 hand.

15 And we are recommending that someone who
16 should and is taking HRT, should take alendronate.
17 Similarly, I don't think it's appropriate to recommend
18 that, for the person who either chooses or the
19 physician agrees alendronate is a better choice,
20 should be required to take HRT.

21 DR. NEW: But the statement that Dr. Jules
22 -- or that Dr. Hirsch proposed, which is not receiving
23 up-front in your first indication does not interfere
24 with the reimbursement --

25 DR. GOLDMANN: Right.

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1 DR. NEW: Okay, that's what I needed to
2 know.

3 DR. KREISBERG: There's a terminology that's
4 used here that I think is wrong. We don't require
5 patients to take anything. Patients make decisions
6 based on our educating them about the pros and the
7 cons. And if I'm going to be sitting down with a
8 woman for the very first time with the issue of
9 preventing bone mineral loss I'm going to be saying to
10 her, there are two ways that we can go on this.

11 One way is with estrogen replacement therapy
12 and here are the pros and here are the cons. And if
13 you have a problem with that for one reason or another
14 there is another drug that appears to be as good as
15 estrogen in protecting the skeleton without the other
16 effects. And the patient decides -- and the implica-
17 tion from some of the discussion that's gone on here
18 is that we actually tell patients what to do.

19 DR. HIRSCH: I agree with that. I think we
20 should tell them. But we should tell them the plain
21 truth that what this drug is for is for X, Y, Z
22 patient -- just describe that. For a woman, post-
23 menopausal, not on estrogen. That's it.

24 DR. KREISBERG: Well, I don't think women
25 have to have a trial on estrogen to become candidates

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1 but I --

2 DR. HIRSCH: I agree.

3 DR. KREISBERG: -- think women have to
4 realize that there are two therapies.

5 DR. HIRSCH: Agreed. I mean, that's what
6 that says. You can do it this way or that way. Could
7 I ask another question that's going to help?

8 ACTING CHAIR CRITCHLOW: Please.

9 DR. HIRSCH: Is there any knowledge about
10 the relative toxicity of two-and-a-half versus five
11 milligrams? Is there anything we should know about,
12 evidence of any kind?

13 DR. DAIFOTIS: When we look at the two-and-
14 a-half and the five milligram dose -- we specifically
15 looked, and that's why I showed you the slide in my
16 talk. We can go back to that actual slide again. I
17 looked to try to see if I could find the difference.
18 I couldn't find the difference so I can't tell you
19 that I'm able to see that at this time.

20 DR. HIRSCH: Right. There's nothing we know
21 about that?

22 DR. DAIFOTIS: No.

23 ACTING CHAIR CRITCHLOW: Are there other
24 safety or toxicity issues? Taking comments on
25 questions 5 and 6 -- although Dr. Troendle said these

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1 data were specific to a different supplement to the
2 IND than we're considering here -- we're still being
3 asked to --

4 DR. TROENDLE: We're considering both.

5 ACTING CHAIR CRITCHLOW: Is this --

6 DR. TROENDLE: Both are being considered
7 today, that's why the questions are here.

8 ACTING CHAIR CRITCHLOW: Okay. Given what
9 we've been presented with as far as the FIT data, are
10 there any comments or issues with respect to efficacy
11 or other issues on the data that we've seen? No?
12 None?

13 With respect to comments about the label,
14 has that been adequately discussed or are there other
15 remaining comments there? Does the committee feel
16 ready to vote on the questions or are there -- Dr.
17 Illingworth.

18 DR. ILLINGWORTH: Just one additional
19 suggestion for the labeling. To add in terms of risks
20 would be something like addition, use of drugs known
21 to accelerate bone resorption. That may be something
22 that physicians might want to use for justification of
23 use of this drug in specific patients. Don't know how
24 the Agency feels about that.

25 DR. SOBEL: That's a question that I think

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1 will require study. For example, in patients taking
2 corticosteroids, the dynamics of the production of
3 osteoporosis perhaps are not amenable to treatment by
4 alendronate.

5 I don't know if the pathology or the effect
6 on osteoclasts and osteoblasts are similar in that
7 kind of osteoporosis, and perhaps alendronate is not
8 the best idea, the best drug, and that will await
9 study. And the company apparently is working on that
10 very issue. They may wish to comment.

11 DR. DAIFOTIS: We have a study -- two
12 studies, actually -- enrolling over 500 patients.
13 They range in age from 17 to 81; they have diseases
14 commonly used to treat -- glucocorticoids; they are
15 taking astrinates -- talked about seven-and-a-half
16 milligrams or higher; they have a variety of non-
17 steroidal, anti-inflammatory drug use; and we will be
18 waiting for information.

19 At this time the study is still blinded.
20 What I can tell you is I was able to look at serious
21 adverse experiences and they do very well, especially
22 with regard to the gastrointestinal tract, which is
23 where I specifically looked at. But we have to wait
24 for the actual data to be available.

25 ACTING CHAIR CRITCHLOW: Are there other

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1 questions? Dr. Colley.

2 DR. COLLEY: So that will be a separate
3 indication then, and not just an additional risk
4 factor?

5 DR. SOBEL: I believe that it's different
6 enough so it's a separate issue.

7 ACTING CHAIR CRITCHLOW: Are there other
8 questions of the Agency, or by the Agency, that should
9 be discussed prior to the voting?

10 The first question: Do results of con-
11 trolled clinical trials provide substantial evidence
12 (by BMD) that alendronate is effective in prevention
13 of osteoporosis in post-menopausal women? I'll start
14 with Dr. Hirsch.

15 DR. HIRSCH: Would you permit a change in
16 the words of this or do we have to absolutely --
17 because I thought we had sort of -- talking about that
18 alendronate is effective in reducing bone loss in --
19 I mean, what do you want to do about that issue? In
20 other words, must I be very strict and say no about
21 this --

22 ACTING CHAIR CRITCHLOW: You can either
23 suggest changes in wording or we can vote with
24 appropriate caveats. Is that acceptable to the
25 Agency?

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1 DR. HIRSCH: Whatever you want.

2 DR. SOBEL: Well, I have two thoughts. One
3 is that you vote on the question as worded and if you
4 have, you know, problems to substitute the bone loss.
5 My second thought is for Dr. Molitch to defend that.

6 ACTING CHAIR CRITCHLOW: Dr. Molitch, do you
7 care to --

8 DR. MOLITCH: The question that I brought up
9 before, my own thinking was that there was enough
10 evidence that gates us from step A to B to C, that I
11 would be able to accept that in fact, we're preventing
12 osteoporosis if we prevent bone loss. I mean, that's
13 the position that, at least I think is reasonable.

14 ACTING CHAIR CRITCHLOW: And is language
15 such as that in terms of evidence in preventing bone
16 loss -- or at least adequate bone mineral density --
17 is sufficiently related to subsequent risk of fracture
18 -- if that were clear and the indication were worded
19 as such, would that be appropriate?

20 DR. HIRSCH: Well, let me just state the
21 thing that I will vote on and say yes, and then the
22 other thing I'll abstain from, or whatever it is that
23 you want me to do.

24 What I want to say yes is: Do results of
25 controlled clinical trials provides substantial

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1 evidence (by BMD) that alendronate is effective in
2 reducing bone loss in post-menopausal women not on
3 estrogen replacement? And my answer is yes, and
4 anything else I will abstain from or something, or say
5 no or whatever you want me to do. Because I disagree
6 with the others. But if those two things are put in
7 I agree with it.

8 ACTING CHAIR CRITCHLOW: Is that acceptable
9 --

10 MS. REEDY: So noted.

11 DR. HIRSCH: Or no. I mean, I do not agree
12 with this statement. I agree with the statement I
13 made --

14 DR. SOBEL: I think we can deal with parsing
15 it out --

16 DR. HIRSCH: Okay, fine. I mean, you see
17 the point is --

18 DR. SOBEL: I see your point and we'll parse
19 it out --

20 DR. HIRSCH: I'm not very excited about it
21 one way or another, I just --

22 DR. SOBEL: I think it's clear to run
23 through on the existing wording of the question, but
24 I understand if osteoporosis remains in you abstain.

25 ACTING CHAIR CRITCHLOW: I mean, I think

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1 it's more helpful for the --

2 DR. SOBEL: Well, and the estrogen issue,
3 but --

4 DR. HIRSCH: Right. I'm just trying to --

5 DR. SOBEL: -- the estrogen replacement
6 will, of course, come into play.

7 ACTING CHAIR CRITCHLOW: I mean, I think the
8 comments are at least as helpful as whatever the
9 absolute vote is.

10 DR. SOBEL: Yes.

11 DR. HIRSCH: Okay, fine. I mean, I don't
12 care. Or say yes to both, whatever you wish me to do,
13 just so long as those two matters are considered.

14 DR. SOBEL: I just want to be able to, you
15 know, get a good sense of --

16 DR. HIRSCH: Good. Well, those are the two
17 points I wish to make about them.

18 DR. SOBEL: All right.

19 ACTING CHAIR CRITCHLOW: And Dr. New.

20 DR. NEW: I wondered if I could propose a
21 compromise and the end of the question would be --
22 well, the answer would be: controlled clinical trials
23 provide substantial evidence (by BMD) that alendronate
24 is effective in reducing bone loss and perhaps
25 preventing osteoporosis in post-menopausal women not

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1 receiving estrogens.

2 How about you, Bob?

3 DR. KREISBERG: I'm going to vote yes
4 anyway. I mean, I think this has boiled down to a
5 semantic issue. I don't happen to agree with the
6 Agency or with Mark, but I don't think it's important
7 enough to vote no on, okay? So the answer is, I'll
8 take whatever you have. It's yes.

9 ACTING CHAIR CRITCHLOW: Dr. --

10 DR. NEW: I must say, I would insist on the
11 absence of estrogens in that first statement.

12 ACTING CHAIR CRITCHLOW: Although the data
13 that we were presented was among women without --

14 DR. NEW: That's what I mean. That the
15 evidence is that it reduces bone loss in women not on
16 estrogen.

17 ACTING CHAIR CRITCHLOW: Dr. Colley.

18 DR. COLLEY: I would agree with comments of
19 Drs. Hirsch and New in changing the wording on that,
20 although the guidelines do use bone density as an
21 endpoint that's appropriate for prevention. Based on
22 that I could say yes, so regardless, either way. But
23 I think the specificity of the wording would be
24 helpful.

25 ACTING CHAIR CRITCHLOW: Dr. Illingworth.

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1 DR. ILLINGWORTH: I would say but with a
2 revision to -- you said effective in prevention of
3 osteoporosis. I would vote in favor of reducing the
4 risk of osteoporosis, because that's what you're
5 doing. Because as data we've shown on the fracture
6 intervention trial, it doesn't eliminate the risk to
7 zero; it reduces the risk.

8 ACTING CHAIR CRITCHLOW: That's a good
9 point. Dr. Molitch.

10 DR. MOLITCH: Yes.

11 ACTING CHAIR CRITCHLOW: And Dr. New.

12 DR. NEW: Yes, with the modification.

13 ACTING CHAIR CRITCHLOW: I vote yes and
14 agree with Dr. Illingworth.

15 Two is directed toward: How should the
16 target population be defined for the pharmacologic
17 prevention of osteoporosis? a) is there a level of
18 bone mineral density that should be considered
19 diagnostic of significant potential risk?

20 Dr. New.

21 DR. NEW: I don't think I'm capable of
22 answering that question.

23 ACTING CHAIR CRITCHLOW: Dr. Molitch.

24 DR. MOLITCH: I would not like to put a
25 number in this by any means, but I would like to at

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1 least see it on the negative side.

2 ACTING CHAIR CRITCHLOW: Dr. Illingworth?

3 DR. ILLINGWORTH: Yes, I would agree with
4 the -- perhaps one standard deviation below the age
5 adjusted mean, or the mean in young women. But again,
6 I have reservations about putting numbers on it just
7 because of the implications for managed care organiza-
8 tions denying coverage.

9 ACTING CHAIR CRITCHLOW: Dr. Kreisberg.

10 DR. KREISBERG: I can't answer that ques-
11 tion.

12 ACTING CHAIR CRITCHLOW: Dr. Colley.

13 DR. COLLEY: I can't answer that either.

14 ACTING CHAIR CRITCHLOW: And --

15 DR. HIRSCH: I'll pass on that one. I can't
16 answer it; I don't have enough information.

17 ACTING CHAIR CRITCHLOW: I have to agree,
18 this is an extremely difficult question to answer as
19 a yes or no. Clearly, bone mineral density is
20 important but we're not considering the interplay of
21 that with other risk factors here so I don't believe
22 that can be answered specifically, either.

23 b) Should all women who are post-menopausal

24 --

25 DR. HIRSCH: I think we have a consensus,

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1 however --

2 ACTING CHAIR CRITCHLOW: That that was --

3 DR. HIRSCH: -- in the sense that low bone
4 density --

5 ACTING CHAIR CRITCHLOW: Clearly.

6 DR. HIRSCH: -- is a significant hazard, or
7 something like that, but we still want to get into
8 numbers. It's at the point --

9 DR. TROENDLE: We don't want numbers. We
10 just want to know if the concept of doing this by bone
11 density is appropriate.

12 ACTING CHAIR CRITCHLOW: I think, unless I'm
13 mistaken, the committee agrees that bone mineral
14 density is something that's important, but in terms of
15 establishing a criteria or whatever, is not possible.

16 DR. HIRSCH: Exactly. I think we've reached
17 sort of a hazard interalia among, you know, many other
18 things, but it's one of the hazards.

19 ACTING CHAIR CRITCHLOW: b) Should all
20 women who are post-menopausal, younger than 60 years
21 of age, and have low bone density be treated prophylactically?
22 lactically?

23 Dr. Hirsch.

24 DR. HIRSCH: I would say no.

25 ACTING CHAIR CRITCHLOW: Dr. Colley.

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1 DR. COLLEY: No.

2 ACTING CHAIR CRITCHLOW: Dr. Kreisberg.

3 DR. KREISBERG: Yes.

4 ACTING CHAIR CRITCHLOW: Dr. Illingworth.

5 DR. ILLINGWORTH: I would say yes, but with
6 the caveat, offered treatment.

7 DR. COLLEY: If I could --

8 ACTING CHAIR CRITCHLOW: Would you like to
9 --

10 DR. COLLEY: We went back to this question
11 before in clarification. I think the wording in the
12 labeling of being considered for treatment is more
13 helpful than "should all". I think the "all" steers
14 me away.

15 DR. HIRSCH: I think the same thing --

16 ACTING CHAIR CRITCHLOW: I agree.

17 DR. HIRSCH: -- and I wasn't rejecting the
18 whole thing out of hand or anything, but simply that
19 I would have wanted to say that those were post-
20 menopausal women not on estrogens and this would be
21 considered as a strong indication for essential
22 treatment or something like that, rather than this
23 fiat that everybody should be treated.

24 ACTING CHAIR CRITCHLOW: Dr. Molitch.

25 DR. MOLITCH: I would agree that all women

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1 should be considered for prophylactic treatment.

2 ACTING CHAIR CRITCHLOW: Dr. New.

3 DR. NEW: I agree, and I would leave the 60
4 years out.

5 ACTING CHAIR CRITCHLOW: I would agree in
6 that women should be either considered or offered
7 treatment or a therapy decision should be at least
8 evaluated, but with the wording "all" in there I would
9 have to say no.

10 c) Should other risk factors such as family
11 history, small body build, or early menopause be used
12 to determine the need for preventive therapy instead
13 of bone density measurement?

14 Do you mean "instead of" as opposed to "in
15 addition to"?

16 DR. SOBEL: I think it's not "instead of"
17 but is it just one factor among others as been stated.
18 It's not "all". You know, it doesn't knock all the
19 other ones out.

20 ACTING CHAIR CRITCHLOW: I mean, I would
21 say, "along with".

22 DR. SOBEL: Along with -- unless you feel a
23 positive finding on bone mineral density is counter-
24 vailing against all other considerations.

25 ACTING CHAIR CRITCHLOW: Dr. New, do you

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1 have a --

2 DR. NEW: If we just say in addition to, or
3 whatever, my answer is yes.

4 ACTING CHAIR CRITCHLOW: Dr. Molitch.

5 DR. MOLITCH: With that last clarification
6 I would say yes; that if the bone mineral density is
7 countervailing against these other risk factors and
8 you had somebody who was 120 percent of young women at
9 age 70, then I certainly would not treat such a woman
10 no matter what her risk factors.

11 DR. NEW: May I clarify that, Dr. Molitch?
12 You're saying that the laboratory test is better than
13 the history, the physician and everything else?

14 DR. MOLITCH: Yes.

15 DR. NEW: Okay.

16 ACTING CHAIR CRITCHLOW: Dr. Illingworth.

17 DR. ILLINGWORTH: I would say that these
18 other risk factors should be included in the assess-
19 ment of the patient to decide on the benefits of
20 treatment. So it's in addition to bone density
21 measurement if that is available. If it's not
22 available then these obviously would be important to
23 consider.

24 ACTING CHAIR CRITCHLOW: Dr. Kreisberg.

25 DR. KREISBERG: I agree with Dr. Illing-

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1 worth.

2 ACTING CHAIR CRITCHLOW: Dr. Colley.

3 DR. COLLEY: I agree with Dr. Illingworth.

4 DR. HIRSCH: I agree with Dr. Illingworth.

5 ACTING CHAIR CRITCHLOW: As do I. Should
6 alendronate be recommended for women who are candi-
7 dates for hormone replacement therapy?

8 Should we address this as a separate
9 question, or has that been essentially folded into our
10 answer to b)?

11 DR. SOBEL: I think you've really addressed
12 it unless you want to amplify a bit on the issue of
13 the candidacy. I don't know how much more we can get
14 out of discussion on this.

15 ACTING CHAIR CRITCHLOW: Is that agreeable
16 to the committee?

17 (Chorus of affirmative answers.)

18 e) Are there other criteria that should be
19 used to determine who should receive alendronate for
20 the prevention of osteoporosis?

21 Dr. Hirsch.

22 DR. HIRSCH: Other criteria than all those
23 mentioned in a), b), c), and d). I mean, no. I mean,
24 I think we've sort of exhausted all of that. I don't
25 think that there are any other criteria that I can

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1 think of -- because we've included family history and
2 so on, body density, measurements, etc. I don't know
3 what --

4 ACTING CHAIR CRITCHLOW: Unless there were
5 other laboratory or --

6 DR. HIRSCH: No, I mean, I have -- unless
7 there are, you know, political reasons or something --
8 I mean, I have no idea -- but no medical or scientific
9 things that I can think of.

10 ACTING CHAIR CRITCHLOW: Are we interpreting
11 the sense of the question correctly?

12 DR. TROENDLE: Yes.

13 DR. HIRSCH: You were looking for another
14 laboratory datum or something of that sort? Another
15 clinical --

16 DR. TROENDLE: Yes. You're saying bone
17 markets, ultrasound -- anything else doesn't factor
18 in. This takes care of --

19 DR. HIRSCH: No -- well, I wouldn't want to,
20 you know -- bone density measured by all of the
21 techniques that are being -- etc., etc. -- and I'm not
22 going to restrict myself to what's currently -- but I
23 have no -- I can't think of any new kind of scientific
24 thing that we haven't discussed that should be put in
25 here.

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1 ACTING CHAIR CRITCHLOW: Dr. Colley.

2 DR. COLLEY: No.

3 ACTING CHAIR CRITCHLOW: Dr. Kreisberg.

4 DR. KREISBERG: No, but I think that this
5 should be understood within the context that the "no"
6 doesn't preclude the addition of future diagnostic
7 studies that might be helpful. For instance, if
8 ultrasound actually becomes something that would help,
9 then that might in fact -- the answer would be "yes"
10 if we knew that.

11 DR. HIRSCH: Agreed. Yes, I'd like to amend
12 it, absolutely.

13 ACTING CHAIR CRITCHLOW: So once other
14 criteria are available that reach the status of other
15 accepted --

16 DR. HIRSCH: Are there other currently
17 available criteria or currently whatever. I mean, the
18 answer to that is no.

19 DR. COLLEY: The sponsor showed a slide with
20 their indications for prevention. There was one line
21 that's missing from our copy here. Something along
22 the lines that the presence of such risk factors may
23 be useful in determining whether to treat patients.
24 And I'd like to see that included as it was on the
25 slide.

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1 ACTING CHAIR CRITCHLOW: Dr. Illingworth.

2 DR. ILLINGWORTH: One other criteria that
3 might be worthwhile to include here would be a patient
4 who shows, on two sequential bone density measure-
5 ments, evidence of accelerated bone loss. That would
6 be justification for treatment.

7 DR. HIRSCH: Evidence of what? I'm sorry,
8 I didn't hear you.

9 DR. ILLINGWORTH: A patient who, say has a
10 bone density measurement now and three years from now,
11 and shows accelerated bone loss. That would strike me
12 as an indication -- even though they may have initial-
13 ly, reasonable bone density. But if they're losing it
14 very rapidly that would seen an indication --

15 DR. HIRSCH: I would agree. I'd sort of
16 included possibilities like that, I guess, in my --
17 when I said --

18 DR. NEW: But that's not prevention; that's
19 treatment. Isn't it Roger?

20 DR. ILLINGWORTH: No, if somebody has no
21 bone density and is losing three percent in a year and
22 say has lost 12 percent in two years, that's far
23 greater than what would be anticipated based on the
24 one to three percent -- even in the pre-menopausal
25 period. That person would be somebody in who you

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1 might want to intervene, even though they had initial-
2 ly normal bone density.

3 DR. HIRSCH: Yes, I mean, there are very
4 special -- if you were planning to live in a space
5 capsule for two years I'd say I think you might take
6 -- you know, something like that. I mean, maybe some
7 very unusual events.

8 ACTING CHAIR CRITCHLOW: Dr. Molitch.

9 DR. MOLITCH: No other tests, no.

10 DR. NEW: No.

11 ACTING CHAIR CRITCHLOW: Dr. New -- no as
12 well.

13 Number 3: Do the BMD data on 2.5 and five
14 milligrams of alendronate per day demonstrate that the
15 2.5 milligram dose is an acceptable minimum dose for
16 the prevention of osteoporosis? Alternatively, is the
17 five milligram dose proposed by the sponsor the most
18 appropriate choice for preventive therapy?

19 Dr. New.

20 DR. NEW: The five milligram dose is the
21 most appropriate.

22 DR. MOLITCH: Five.

23 ACTING CHAIR CRITCHLOW: Dr. Illingworth.

24 DR. ILLINGWORTH: Five is most appropriate.

25 ACTING CHAIR CRITCHLOW: Dr. Kreisberg.

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1 DR. KREISBERG: I agree.

2 ACTING CHAIR CRITCHLOW: Dr. Colley.

3 DR. COLLEY: I would agree with the five.
4 I think it was argued pretty effectively that the 2.5
5 milligram results we saw were best-case scenario.

6 And one thing we haven't really talked much
7 about in terms of patients taking this is, although
8 the adverse effect profile is not that severe, the
9 compliance issue of having to take the drug at a
10 certain time and day, waiting before they have their
11 cup of coffee in the morning -- it's something that
12 over decades, it's a lifestyle change that people are
13 going to have to be very careful to adhere to.

14 And as a result I think there is going to be
15 some loss of compliance and the five milligram dose
16 would be more appropriate.

17 ACTING CHAIR CRITCHLOW: Dr. Hirsch.

18 DR. HIRSCH: Five.

19 ACTING CHAIR CRITCHLOW: And I say five as
20 well.

21 Number 4: Taking into consideration the
22 overall benefits and risks, do you recommend that
23 alendronate be approved for prevention of osteoporosis
24 in post-menopausal women?

25 Dr. Hirsch.

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1 DR. HIRSCH: Yes, again, I just don't want
2 to get involved in the verbiage of the whole thing,
3 but the sentiment is yes. I mean, post-menopausal
4 women not on hormonal replacement, etc., etc -- all of
5 the caveats we've sort of gone through and do under-
6 stand.

7 ACTING CHAIR CRITCHLOW: Dr. Colley.

8 DR. COLLEY: Yes.

9 ACTING CHAIR CRITCHLOW: Dr. Kreisberg.

10 DR. KREISBERG: Yes.

11 ACTING CHAIR CRITCHLOW: Dr. Illingworth.

12 DR. ILLINGWORTH: Yes.

13 ACTING CHAIR CRITCHLOW: Dr. Molitch.

14 DR. MOLITCH: Yes.

15 ACTING CHAIR CRITCHLOW: And Dr. New.

16 DR. NEW: Yes.

17 ACTING CHAIR CRITCHLOW: And -- yes.

18 Five: Do results of the vertebral fracture
19 (FIT) study and those of the U.S./Multinational post-
20 menopausal osteoporosis treatment studies provide
21 substantial evidence that alendronate is effective for
22 prevention of vertebral, hip, and wrist fractures?

23 Dr. New.

24 DR. NEW: Well, it was clarified to me now
25 that these women were on a very -- they were on

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1 estrogens before they started alendronate, is that
2 right?

3 DR. HIRSCH: No, no -- only one subgroup
4 was.

5 DR. NEW: Then maybe I misunderstood Dr.
6 Goldmann. Can you clarify that for me? I'm talking
7 about that table 7 here.

8 DR. YATES: Can I just clarify? The two
9 populations that we studied. For the fracture risk
10 reduction we looked at women who were in one -- in the
11 fracture intervention trial they had previous verte-
12 bral fractures -- that was that arm of the fracture
13 intervention trial.

14 In the phase III study population they did
15 not have vertebral fractures at baseline except the 20
16 percent. And none of the women in those two studies
17 where we looked at fracture risk reduction were on
18 estrogen during the trial or prior to the study. We
19 have a different study ongoing for that.

20 DR. NEW: Well, I guess I would say yes.

21 ACTING CHAIR CRITCHLOW: Dr. Molitch.

22 DR. MOLITCH: Yes.

23 ACTING CHAIR CRITCHLOW: Dr. Illingworth.

24 DR. ILLINGWORTH: Also, a yes.

25 ACTING CHAIR CRITCHLOW: Dr. Kreisberg.

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1 DR. KREISBERG: Yes.

2 ACTING CHAIR CRITCHLOW: Dr. Colley.

3 DR. COLLEY: Yes.

4 ACTING CHAIR CRITCHLOW: Dr. Hirsch.

5 DR. HIRSCH: Yes.

6 ACTING CHAIR CRITCHLOW: And yes for me as
7 well.

8 Taking into consideration the overall
9 benefits and risks, do you recommend that alendronate
10 be approved for prevention of fractures of the spine,
11 hip, and wrist in post-menopausal women with pre-
12 existing vertebral fractures?

13 Dr. Hirsch.

14 DR. HIRSCH: Yes, with all -- again, the
15 statements we've made before. Yes.

16 ACTING CHAIR CRITCHLOW: Dr. Colley.

17 DR. COLLEY: Yes.

18 ACTING CHAIR CRITCHLOW: Dr. Kreisberg.

19 DR. KREISBERG: Yes.

20 ACTING CHAIR CRITCHLOW: Dr. Illingworth.

21 DR. ILLINGWORTH: Yes.

22 ACTING CHAIR CRITCHLOW: Dr. Molitch.

23 DR. MOLITCH: Yes.

24 DR. NEW: Yes.

25 ACTING CHAIR CRITCHLOW: Yes.

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1 Do you recommend changes in the material
2 proposed by the sponsor for incorporation into the
3 Indications and Usage section? Is there any need to
4 incorporate further safety information based on the
5 submitted studies?

6 Dr. New.

7 DR. NEW: I thought that we had just gone
8 over that -- all the things -- my answer to that is,
9 refer to one.

10 ACTING CHAIR CRITCHLOW: May I ask the
11 Agency if we should do a roundtable on this?

12 DR. TROENDLE: You might just ask if anyone
13 has any suggestions and ask if they're not satisfied.

14 ACTING CHAIR CRITCHLOW: I'll just ask each
15 if there are any additional comments one might want to
16 make. Dr. New, no. Dr. Molitch.

17 DR. MOLITCH: I have no additional comments.

18 ACTING CHAIR CRITCHLOW: Dr. Illingworth.

19 DR. ILLINGWORTH: No, I think the proposed
20 indication reads nicely and is sufficiently open to
21 allow clinicians to use clinical judgment in who to
22 treat.

23 ACTING CHAIR CRITCHLOW: Dr. Kreisberg.

24 DR. KREISBERG: Only to re-emphasize that I
25 think the relationship to estrogen should be clari-

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1 fied, sharpened, in the material.

2 ACTING CHAIR CRITCHLOW: Dr. Colley.

3 DR. COLLEY: I would agree with Dr. Kreis-
4 berg on that issue.

5 ACTING CHAIR CRITCHLOW: And Dr. Hirsch.

6 DR. HIRSCH: Agree with Dr. Kreisberg.

7 ACTING CHAIR CRITCHLOW: I don't think I
8 have any further information although I'm sure there's
9 a statement in there with respect to showing adequacy
10 of calcium and vitamin D nutrition. And if that's not
11 in there that's probably a statement that should be
12 made.

13 Just in closing, I think -- and the commit-
14 tee please correct me if I make a misstatement here --
15 I think all felt that alendronate would be a useful
16 addition to women who are in need of reducing bone
17 mass. It obviously was a unanimous decision that
18 alendronate should be recommended for approval for
19 prevention of bone loss theoretically related to
20 decreasing the risk of post-menopausal osteoporosis,
21 and that the data that we were presented was consis-
22 tent with preventing or decreasing risk of fracture
23 among women with pre-existing fractures.

24 For the committee there's a meeting tomorrow
25 at 8 a.m., closed meeting. In this room?

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1 MS. REEDY: Yes, in this room.

2 DR. HIRSCH: May we leave books here? Are
3 they safe, or take them with us?

4 MS. REEDY: Yes, you may.

5 DR. HIRSCH: Can leave things here?

6 MS. REEDY: Yes, you may leave things here.
7 And thank you very much, Dr. Critchlow; an excellent
8 job chairing.

9 ACTING CHAIR CRITCHLOW: And thank you,
10 Mark, for a nice presentation and keeping within our
11 time.

12 (Whereupon, Meeting #66 of the Endocri-
13 nologic and Metabolic Drugs Advisory Committee was
14 concluded at 3:30 p.m.)

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C E R T I F I C A T E

This is to certify that the foregoing transcript in
the matter of: Endocrinologic and Metabolic Drugs
 Advisory Committee Meeting #66

Before: DHHS/PHS/FDA/CDER
Date: February 20, 1997
Place: Bethesda, Maryland

represents the full and complete proceedings of the
aforementioned matter, as reported and reduced to
typewriting.

A handwritten signature in cursive script, appearing to read "James G. ...", is written over a horizontal line.