CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:NDA 19532

ADMINISTRATIVE DOCUMENTS

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUGS AND BIOLOGICS

DATE: JUN 23 1987

FROM: Director, Division of Cardio-Renal Drug Products, HFN-110

SUBJECT: Microx approvability (NDA 19-532) and Zaroxolyn labeling, Pennwalt

TO: Director, Office of Drug Research and Review, HFN-100

Attached are what represents my best shot at completing the action on Microx. I do believe it is approvable. I also believe it is confusing and is not consistent with an orderly market place. I do not, for the life of me, understand why Pennwalt did not work Microx up for edema (although I suspect it was to torture along exclusivity but that is so transparent I cannot really believe it). Microx is a more esthetically pleasing pharmaceutical dosing form than Zaroxolyn and the dose of Microx has been better defined than is the dose of Zaroxolyn. It is, overall preferable to Zaroxolyn, so it should be marketed.

The revised package inserts for both Microx and Zaroxolyn are attached. Several issues remain.

1) The animal carcinogenicity studies that supported the initial approval of Zaroxolyn have been reviewed (see review by Dr. Harris) with the Microx NDA. The original (as well as the current) package insert for Zaroxolyn did not and does not have a statement regarding carcinogenicity. The new Zaroxolyn label, attached, has been brought into conformance with the content and format regulations. So both Zaroxolyn and Microx need to have a statement regarding carcinogenicity and the Zaroxolyn labeling will be newly approved.

As you can see from Dr. Harris' review, both the rat and mouse study were rather poorly done, and according to Dr. Resnick "meet nobody's standards then or now." We have not been able to find, in the Division's files, prior pharmacology reviews nor an SBA. We do not know what the judgments regarding the studies were at the time of initial approval. Whatever was thought, did not prohibit marketing then and does not now. However, the labeling should be consistent with what exits in the Pennwalt submission.

2) I am not turned on by using 1/2 instead of 0.5 for dosing references in the package insert. Pennwalt claims that coexistence of Zaroxolyn (with a usable dose of 5.0 mg) and Microx (with a usable dose of 0.5 mg) is a set-up for confusion and consequently, wish to educate physicians to use 1/2 when prescribing Microx.

I guess what bothers me is that a rather transparent commercial endeavour, which will introduce confusion into the marketplace, and in order to help minimize the confusion requires a change in scientific notation. That is the wrong driving force and I would not allow it.

However, I recognize that such a position would be rather rigid and, therefore, I defer to your choice. Replace all 1/2s with 0.5s except for the 1/2 stamped onto the pill, or leave it alone.

3) The DO NOT SUBSTITUTE, as it is written, is not appropriate since it implies no generic substitution at all. This definitely needs revision.

4) The rest of the package insert for Microx and Zaroxolyn are acceptable to me, and are better than what exists. But each could still be better.

Completely unedited versions of both inserts are attached. I suggest the following words for the DO NOT INTERCHANGE and carcinogenicity, respectively.

DO NOT SUBSTITUTE

Zaroxolyn tablets and other formulations of metolazone, which share its slow and poor bioavailability (compared to an oral solution of metolazone), are not therapeutically equivalent at comparable doses to Microx which is more rapidly and completely bioavailable (compared to an oral solution). Formulations bioequivalent to Zaroxolyn and formulations bioequivalent to Microx should not be substituted for each other.

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY: Mice and rats given metolazone for 1 1/2 to 2 years at daily doses of 2, 10 and 50 mg/kg (approximately 13, 67 and 333 times the average human dose of 0.15 mg/kg) showed no evidence that metolazone caused an increased number of tumors. The small number animals studied or of surviving animals that had histological examination of tissues was so small that no definitive statement regarding carcinogenic potential can be made.

The releasable reviews are okay as a SBA. The SBA that was developed is not necessary.

Raymond J. Lipicky, M.D.

Attachments

cc: Orig. NDA
HFN-110
HFN-110/CSO
HFN-110/RLipicky:6/25/87:6/27/87
ef:6/25/87:6/26/87:sb:6/29/87:#0979g

M E M O R A N D U M

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drugs and Biologics

Date : January 23, 1987

From : Director, Office of Drug Research and Review (HFN-100)

Subject: NDA 19-532, Microx (metolazone) and NDA 17-386/S-015 (metolazone labeling revision)

To : Director, Division of Cardio-Renal Drug Products (HFN-110)

I have a few thoughts about both the labeling revision and Microx.

I. Labeling revision for Zaroxolyn

A. Indications

I take it that the current statement of indications is now standard (Esidrix and Diuril share it); if we have been allowing that language in recent labeling revisions I would not necessarily propose altering it now, but the implication that metolazone "enhances the effectiveness" of other agents, as opposed to contributing its own effect additively is premature. Why not use the same indication you propose for Microx?

I note labeling of Zaroxolyn still includes hypertension. Is that what you intended or was only Microx to have this claim?

B. Changes proposed in Pennwalt September 26, 1986 letter.

I presume these have not been accepted; I agree.

C. Warnings

Are these paragraphs more or less standardized for diuretics? They should be, I think, and this may be the right moment. Note that the paragraph on hypokalemia does not stress dose-relatedness, and that the archaic reference to ganglionic blockers persists.

I do not agree with removal of The Warning No 7 to Precautions. It deserves a warning.

As with other drugs, the Warnings section would be much clearer if each section were titled: Hyponatremia, Hypokalemia, Azotemia, etc.

D. Precautions

1. The fact that an increase U.A. is usual, that abnormal values are common, and that (as with all these drugs) gout can be precipitated even in patients lacking a prior history, is not made clear.

2. The furosemide interaction can be mentioned here but should reference Warnings too.

3. There is no clear statement that glucose tolerance is impaired. In fact, paragraph 3 almost denies it. Are there data on this?

4. Do we really think diuretic dose needs to be reduced when triamterene or amiloride are initiated?

5. The proposed version of the Carcinogenesis section seems unusual; perhaps there is more information that would explain it. The mouse and rat studies were obviously thought adequate at the time of approval. Even if they fall short of the most modern standards they do not necessarily give no information. I would suggest a revision that acknowledges what was done and gives its limitations, e.g., use of less than MTD, smaller than current number of animals, etc. I do not think we should re-label drugs as inadequately tested whenever we modify our standard.

E. ADRs

They have managed not to mention impotence, either as reported to them or as reported with other diuretics, but we know it does occur.

F. D + A

Here or elsewhere the dose-responsiveness of hypokalemia should be noted.

II. Microx

As is not unusual, the two Microx studies do not give unequivocal dose-response information, but a few points seem clear: 1) Neither study suggests any basis for use of a daily dose above 1 mg; 2) 0.5 mg is a reasonable initial dose, but probably not a full-effect dose in many patients; it causes clear K loss; it should probably be thought of as similar to 12.5 mg of chlorthalidone. Less clear, but probably, the 2.5 mg dose of Zaroxolyn seems likely to represent a maximum useful dose; it certainly causes at least as much K loss as 1 or 2 mg of Microx. It seems possible that the slightly shorter action of Microx does allow more K recovery but this hardly supports a claimed advantage; being better than

"yourself" does not amount to much and the main implication of a difference would be that the Zaroxolyn formulation should not be used for hypertension. The question is how Microx compares to other diuretics and without further evidence no "less K-loss" claim seems appropriate. I cannot help adding that despite what "recent reports" (MOR p. 19) say, the effects of all doses of metolazone on Serum K are fully developed by week 2 (the first assessment) and the BP effect also seems complete (Study LDM-102, with placebo) by 2 weeks.

A. Labeling

1. The increased detail in Clinical Pharmacology is in the right direction but I think it goes too far in giving specific numbers and values (e.g., study numbers and mean values to the tenths of mmHg. It also seems to imply, although the table doesn't, that there is a dose-related response all the way to 2 mg, which is really not the case. The lack of increased BP response to 2 mg should be emphasized. Also, given the lack of placebo in study LDM-101, it is not possible to say how much effect was due to drug. I do not believe the maximum effect of drug can be said to have occurred at 4-6 weeks. In LDM-102, where placebo allows you to judge spontaneous change there is no significantly greater drug-placebo difference at six weeks than at two. E.g., for 1 mg.

	2	4	6
Change DBP: Drug	6.8	9.7	8.0
Placebo	2.7	3.0	4.3
Difference	4.1	6.7	3.7
Change SBP: Drug	12.7	15.3	12.8
Placebo	4.4	2.9	5.9
Difference	8.3	12.4	6.9

I cannot say an increased response over time is ruled out but it surely is not supported, and labeling should not assert it occurs. I believe there is a great deal of evidence in our files that the full response to diuretics is attained within 2 weeks, probably less. Some day, when we have lots of free time, we could explore that issue.

2. Does the clinical pharmacology section represent some standard or "class" outline or specific language? The first paragraph seems to overdo the idea of unknown mechanism. Surely the fact that all diuretics are also antihypertensives tells us something. Perhaps there is a way to be a little less uncertain, e.g., "The precise mechanism through which diuretics lower BP is uncertain but is presumed to be related to their saluretic and diuretic properties."

3. "Clinical hypokalemia" is not defined (p. 2) and, again, the table is over specific. What you want, I think, is something like: "The mean changes in serum K were 0.4 mEq/L at the 0.5 mg dose and 0.6 mEq/L at the 1.0 mg. Hypokalemia (serum K less than 3.5 mEq/L occurred in about _____% at 0.5 mg and _____% at 1 mg." One could add another value for hypokalemia with symptoms, although despite allowing it for amiloride I don't think it's very relevant. I note Pennwalt's complaint that these figures are not given in other thiazide labeling, but we should probably alter that. From Maxzide studies we have such figures for HCTZ and probably have similar data on other agents if we look. Loop diuretics to date, all very short-acting, pretty clearly do produce less hypokalemia.

The material on p. 3 is also over-specific. There is no good reason to separate the two studies and the specific facts cited are oddly chosen: Mean serum K is not a very useful figure in this setting. One could add to the statement in the previous paragraph "and occasional serum K values below 3mEq/L were seen in all dose groups. Serum uric acid increased by an average of 1 mg/dl while serum sodium and chloride and BUN were minimally altered."

4. The indications section here is fine. Shouldn't Zaroxolyn get the same words.

Do you want to discourage use of Microx in CHF quite so strongly? After all, the dose of 0.5 to 1.0 mg is not potentially dangerous and certainly has some effect. Wouldn't it suffice to say: "Microx tablets have not been evaluated for the treatment of fluid retention due to heart failure or renal or hepatic disease (note change in language-renal failure is not usually treated with diuretics, nephrotic syndrome is) and the correct dosage for treatment of these conditions is not established.

5. The Indications section should include the standard pregnancy language.

The section would benefit from titles and better paragraphing.

a. Do we know the origins of the first paragraph? It has long been there, I know, but I am not familiar with the syndrome except perhaps in relation to very rigorous diuresis.

b. Is it time to add to the list of those at risk of hypokalemia, patients with ventricular arrhythmias? Also, why not get all K-related material in one place, including the need for monitoring

and need for treatment of hypokalemia with either dose reduction, K-supplementation, or K-sparing diuretic (never both at once).

c. I am quite sure you do not need a prior history of gout to get gouty attacks on diuretics.

d. The reference to ganglionic blockers seems odd.

e. The first paragraph on p. 6 does not make complete sense. Addition of K-sparing diuretics is not likely to potentiate diuresis much and if it did, which would you reduce the dose of? K-retention and hyperkalemia can occur but they would be very unusual in someone hypokalemic on metolazone alone. And is the K-sparing diuretic given when "required for the treatment of hypertension" or for hypokalemia?

6.

Precautions

a. Why restate lack of data in edema if it's already in Indications.

b. The "use caution in hyperuricemics" is not helpful. The risk is already described in Warnings.

c. What evidence is there that hypokalemia is "more common in association with prolonged therapy?" All antihypertensive therapy is long-term anyway.

d. This section also badly needs titles. It's very hard to deal with this way.

e. How did the frequency of orthostatic hypotension compare with placebo groups.

f. Metolazone does not "exert measurable effects on glucose metabolism." It impairs glucose metabolism and increases (not affects) insulin requirements or bring on or worsen hyperglycemia and glycosuria.

g. What cumulative effects are seen in patients with severely impaired renal function?

h. The furosemide interaction section doesn't read right.

i. Some of the interactions are new (i.e., not in Zaroxolyn), such as chloramphenicol (is it true) and sympathomimetics (do they decrease metolazone effect or just increase BP) and others are repetitive. Could some of these (curariform drugs, insulin) refer to other sections where they are described in detail.

j. See above re Carcinogenesis section.

7.

Adverse Reactions

The ADR labeling does a very peculiar thing. It bases labeling for a new dosage form of metolazone on 200 patients, ignoring, for the most part, the clinical trial and marketing history of metolazone in other forms. That really doesn't make sense. The labeling more or less says none of the ADRs in the table were really drug-related (admittedly that's what these data are compatible with) but there's a lot of other history with metolazone and other diuretics and these small studies cannot suffice to allow that conclusion. Muscle cramps, weakness, and rash, e.g., are probably drug-related and there seems to be growing evidence that impotence is a consequence of diuretic therapy.

Also, note that the figures for chest pain given in labeling differ from the MOR, where rate in placebo is zero, vs 3.7% in the labeling (1 case of 17).

Labeling should reflect both Zaroxolyn data and the new data, not just the new data. It appears, e.g., that known reactions to Zaroxolyn that did not happen to be seen in 226 Microx exposures are relegated to the last paragraph on p. 14 as reactions with similar agents. It should be possible for Pennwalt to retrieve data on Zaroxolyn from past submissions. An all "placebo-controlled studies" pooled table would be one reasonable display for more common events, or some other analysis of controlled trials could be used, followed by a list of other observed ADRs by body system, something like current labeling. The introductory language in current labeling is far too exculpatory but it is certainly reasonable to say that drug relationship is not certain in all cases. Perhaps better would be to have two lists, one of ADRs considered probably related, a second for ADRs of less probable relationship. Finally a third list of ADRs seen with other drugs is worth including. I should note that I find it difficult to believe that the reactions on the list of ADRs at the bottom of p. 14 have not been reported for metolazone -- I presume they have been reported for Zaroxolyn. In that light, I think the last sentence of the ADR section (p. 15, top) is extremely misleading.

Insert C should not refer to the two mg dose if we omit it. Also, how does the table fit with the table on p. 2 of Insert B? I would think the same material need not be in both places; one could refer to the other.

8. Dosage and Administration

Paragraph 3 is not clear. Paragraph 2 seems to urge a start at 0.5 mg with move to 1 mg if response is insufficient. Paragraph 3 is

either saying don't use the 1 mg, even though BP response is better, because of the worsened hypokalemia, etc., or its saying don't go still higher. If the latter, there's no real reason to go beyond 1 mg, as there is no added effect. The last paragraph is not strong enough; it's not just preferable not to go past one mg. There is no reason at all to do so.

B. Other comments.

1. Your Division Director's Review says that releasable reviews will constitute the SBA but there is also an SBA prepared by Pennwalt that has been somewhat marked up. (My quick scan indicates it would need more work). The reviews would be sufficient, in my view. Which is to be the SBA?

2. I realize I have raised a lot of questions about what could be said to be a small matter, but I think it is simply that I had not looked closely at a thiazide labeling lately. I understood that class labeling or a class outline was imminent. It would help quite a bit.

3. Whatever changes Microx labeling undergoes should probably be made similarly in Zaroxolyn. It seems fairly apparent that 5 mg of Zaroxolyn is an excessive dose in hypertension. Shouldn't labeling say this or omit that claim altogether and refer to their Microx product. I realize other makers of metolazone might object to dropping it entirely but I would expect they would be willing to recommend only the 2.5 mg recommended dose.

4. Regarding the "essentiality" of the trials, we need to be clear on what they were for. As I see it, they established the effectiveness and proper dose of a product with kinetic characteristics like those of Microx, which are different from those of Zaroxolyn. We also know that the studies are new (not used to support a previous claim) and Pennwalt-supported.

5. I think, all things considered, I would prefer to sign this one. I see at least some potential for an exclusivity debate. While there are a lot of issues raised above, most have pretty straightforward resolutions and many can be referred to the firm for drafting.

/s/

Robert Temple, M.D.