3 is the following quote, "The pharmacology studies in many of the clinical investigations reported herein were conducted with the single chemical substance described under chemistry. To this substance has been added a subtherapeutic amount of atropine sulfate to discourage deliberate overdose."

Comment

Since up to eight tablets a day are permitted this would include a dose of 1/300 of a grain of atropine sulfate which is within the therapeutic range. Therefore this statement is misleading and incorrect.

I am in the process of reviewing the brochure and the insert.

On page 7 of the brochure under the heading "Children" the following quote: "adequate daily dosage of Lomotil for children is determined by the child's age and is given in the following table":

	Milligrams
"3 to 6 months	3
6 to 12 months	4
1 to 2 years	5
2 to 5 years	6
5 to 8 years	8
8 to 12 years	10."

Comment

As I previously pointed out, the data to substantiate safety and efficacy in infants and children is extremely inadequate and incomplete. The drug was administered in a liquid form instead of in the tablet form as indicated here. There were only 40 individual case histories submitted for children and these were grossly inadequate and incomplete as far as clinical data and laboratory data were concerned. These detailed dosages were not worked out in the NDA.

On page 8 the following quote: "Side effects incidental to Lomotil administration are relatively uncommon."

Comment

This statement is certainly untrue, for instance 10 out of 25 children in one series had side effects. The authors write "Their incidence, in 501 patients as reported by 28 United States investigators, is shown in the accompanying table."

Comment

Actually this table plus the caption unler it indicates that in this 501 patients there were 104 side effects which represent an incidence of over 20%. Furthermore, the side effects were listed in such a way as not to indicate completely the nature. For instance, there were 6 cases of skin eruption noted but it did not state that in this group there was one case of giant urticaria and one case of angioneurotic edema. There was one case of euphoria noted in the footnotes which indicates very clearly the opiatelike effect of this drug.

On page 9 the following quote: "Because of the structural similarity of Lomotil and drugs with a definite addiction potential, Lomotil should be administered with considerable caution to patients who are also receiving such addicting drugs."

Comment

In view of the data in the NDA which demonstrates definitely that Lomotil is a narcotic and has a definite addiction potential, this statement is very misleading. It implies that Lomotil does not have an addiction potential which it obviously does. It imples that Lomotil only has a structural similarity to these other drugs and yet the firm's own data demonstrates that it has a very similar action to codeine and morphine. It differs from these mainly in degree.

In the next paragraph on the same page 9 the following quote: "Finally, competent studies indicate a possible dependency when Lomotil is given in high dosage."

Comment

In view of the previously quoted paragraph referring to addiction, then this reference to dependency is misleading. Furthermore, these competent studies did not indicate a possible dependency when Lomotil is given in high doses, they indicated a definite dependency or addiction. At the bottom of page 9 the authors quote McHardy as stating "I frankly feel that we have satisfactorily disproved the possibility of addiction to R1132."