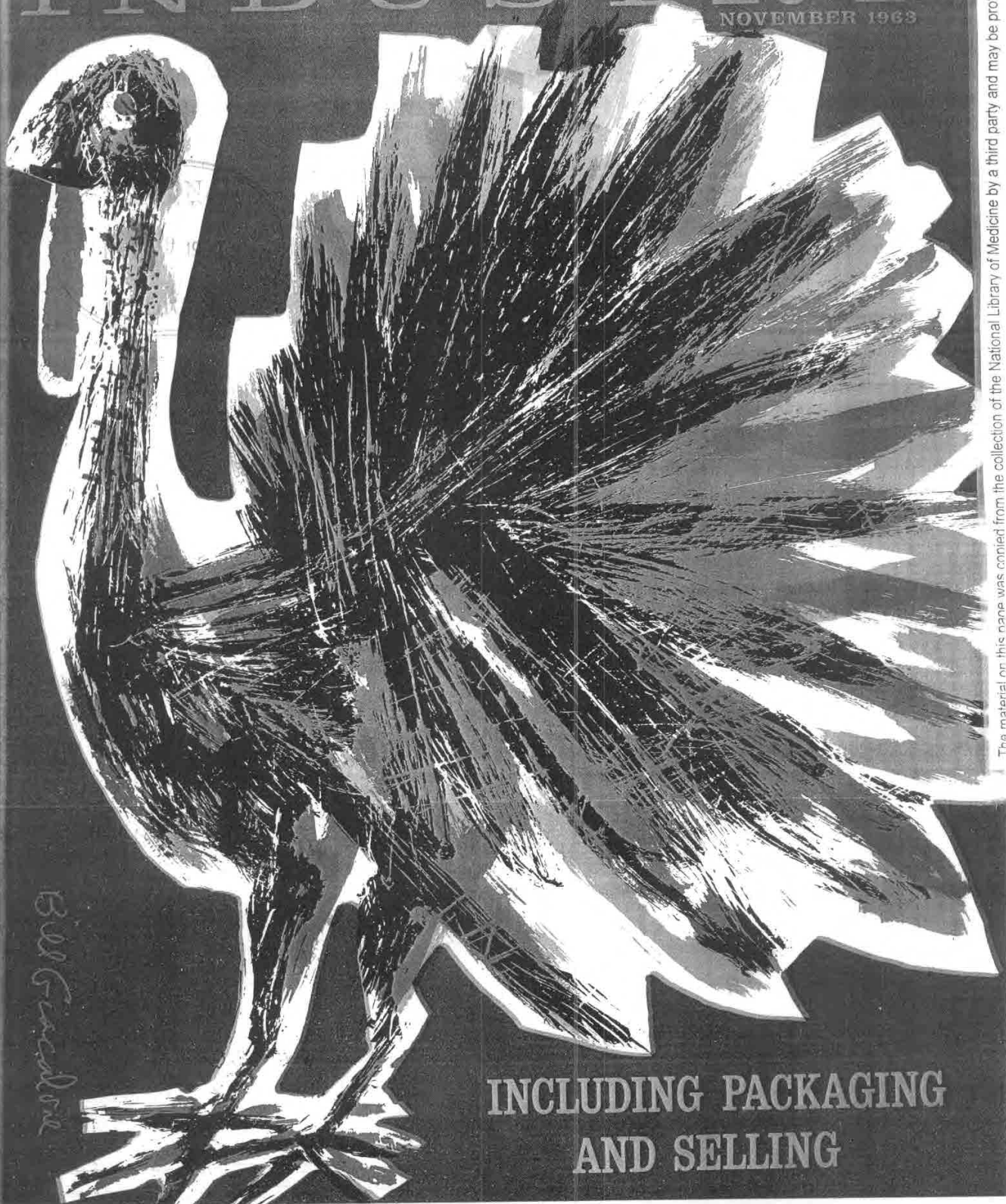


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DRUG & COSMETIC INDUSTRY

NOVEMBER 1963



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Drug and Cosmetic Industry

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PHARMACEUTICAL ASPECTS OF DEXTROMETHORPHAN HYDROBROMIDE, N. F. XI

A SAFE NON - NARCOTIC, EFFECTIVE ANTITUSSIVE

by LOUIS MAGID, Ph. D. HOFFMANN - LA ROCHE, INC.

Dextromethorphan hydrobromide, N.F. XI, is a safe, effective, non-narcotic antitussive, approximately equal in activity to codeine. The effectiveness of dextromethorphan has been demonstrated in clinical appraisals by Cass and Frederik^{1,2,3} in patients suffering from disease entities associated with chronic cough and by Bickerman et al.^{4,5} in citric acid aerosol stimulated cough response in normal human subjects. Clinical evaluation by Ralph⁶ in human pathologic cough showed that dextromethorphan is an effective and safe cough suppressing agent having the antitussive activity of codeine without sharing its addictive properties and without producing the side effects typical of codeine. In a series of double-blind investigations, Cass et al.^{1,2,3} found that dextromethorphan has a specific effect on cough which is equal, if not superior, to that of codeine. Bickerman et al.⁵ observed no statistical difference in the antitussive activity of 10 mg. of dextromethorphan hydrobromide and 15 mg. of codeine. According to Ralph⁶, dextromethorphan takes effect in about twenty minutes and has a good duration of action. Thus, administration of the drug from one to three times daily generally provides effective relief—even when the cough is chronic.

Dextromethorphan has been widely used in prescription-type products and is now approved for OTC use. The Food and Drug Administration removed the prescription legend requirements on dextromethorphan hydrobromide in July 1956. Since that time the use of this non-narcotic antitussive has grown steadily.

Dextromethorphan has become a leader⁶ in the

antitussive field and is rapidly replacing codeine in cough preparations. Of the top fifty proprietary cough syrups, about 15 per cent are made with dextromethorphan and this percentage represents more than 50 per cent of the dollar sales of the leading proprietary syrups. A review of the composition and sales of the leading dextromethorphan cough preparations was presented recently by Kalish⁶.

Cough and cold sales have increased over 40 per cent during the past few years. Narcotic preparations with and without antihistamines have held their dollar sales, but have not increased their dollar volume with the growing market. Several years ago narcotic cough preparations with and without antihistamines accounted for more than two-thirds of the market. A few years later their share declined approximately one-third. If proprietary products are included in this evaluation, the share of the market enjoyed by this group is further lowered by more than 20 per cent. The trend and comparison of sales of the important cough product groups are shown in the following graph.

The above trends are not surprising in view of the side effects common to the opiate derivatives. These toxic effects include anorexia, nausea, vomiting, constipation, drowsiness, headache and vertigo, together with addiction liability, which presents a hazard, particularly in the chronic coughler.

The numerous disadvantages of the opiates prompted the search for a clinically effective, non-narcotic antitussive which was equiactive to codeine. Dextromethorphan was one of the first synthetic non-narcotic antitussive agents. The studies by Isbell and

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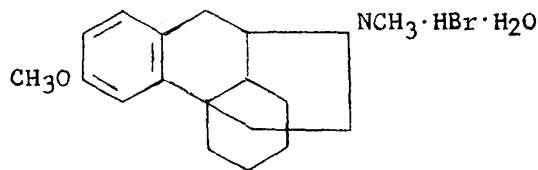
Fraser¹¹ in 1953 demonstrated that dextromethorphan showed no addiction liability. Long-term clinical trials have disclosed no evidence of toxicity⁹. According to Bickerman², Ralph¹⁰ and Cass and Fredrik¹, the incidence of adverse side effects was remarkably low and consisted of occasional drowsiness or gastrointestinal intolerance which appeared to be of the same order of magnitude as that of placebo.

Dextromethorphan has become the antitussive of choice in cough preparations for the following reasons:

- 1—It is non-narcotic
- 2—It is safe and effective
- 3—Excellent stability
- 4—It is approved for OTC sale
- 5—Rapid onset of action
- 6—Adequate duration of action
- 7—Pharmaceutically acceptable for incorporation into various dosage forms.

CHEMICAL PROPERTIES

Dextromethorphan hydrobromide (d-3-Methoxy-N-methylmorphinan hydrobromide) is isolated as the crystalline monohydrate with the empirical formula $C_{15}H_{25}NO \cdot HBr \cdot H_2O$ and a molecular weight of 370.35. The structural formula is as follows:



Dextromethorphan hydrobromide is unaffected by mild oxidizing or reducing agents. It is stable in the cold in 1N HCl or 1N NaOH and is stable in the pH range of 4 to 5.6 under ordinary storage conditions and up to 3 months storage at 45°C. It reacts with

alkalies to form the free base which is insoluble in water. It forms a nitrate of low solubility and is precipitated from aqueous solutions by tannic acid, salicylates and concentrated solutions of iodides. In aqueous solutions it is slowly decomposed on exposure to sunlight. It is incompatible with some of the certified dyes (see section on compatibility).

Physical Properties

Appearance	Crystalline powder
Color	White
Odor	None
Color of solution	Colorless
pH of 1% solution	5.2 - 6.5
Residue on ignition	Max. 0.1%

Solubility

Water at 25°C	About 1.5%
at 50°C	5%
at 70°C	10%
at 85°C	25%
Alcohol, U.S.P.	25%
Glycerin, U.S.P.	10%
Propylene Glycol, U.S.P.	Soluble
Chloroform, U.S.P.	Soluble
NaCl equivalent of 1% solution	0.158%

$$[\alpha]_D^{20} = +26 \text{ to } +28^\circ \text{ (2\% solution in water)}$$

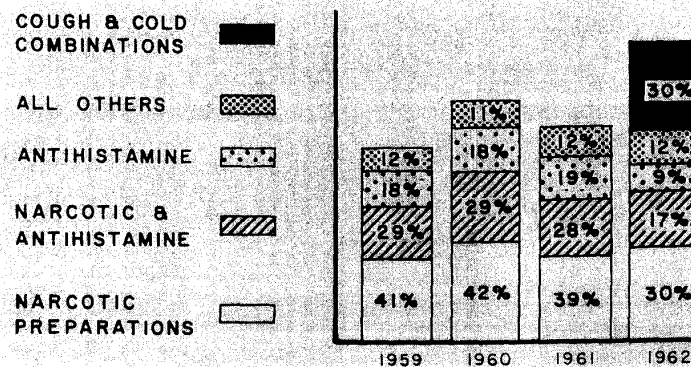
Stability

<i>Crystals</i>	
Light	Stable to normal indoor illumination
Air	Stable
Moisture	Non-hygroscopic

Aqueous Solutions

pH	Stable in pH range of 4 to 5.6
Air	Stable
Light	Stable on exposure to normal indoor illumination. Slowly decomposed on exposure to sunlight.

COMPARISON OF SALES OF THE IMPORTANT COUGH PRODUCT GROUPS



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