

EXPERT REPORT ON THE CLINICAL DOCUMENTATION

1 Introduction

Coltsfoot, Pine & Honey Balsam (Special Mixture No 233) is a product added to the Thornton & Ross range at the request of a pharmacist and has been manufactured by Thornton and Ross for many years. It is a herbal remedy containing traditional ingredients used for the relief of the symptoms of coughs, colds and bronchitis and is administered orally.

This expert report forms part of a submission by Thornton & Ross Ltd to continue to market Coltsfoot, Pine and Honey Balsam (PLRA 0240/5209).

The mixture contains 0.01ml Coltsfoot Liquid Extract, 0.0076ml Ipecacuanha Liquid Extract, 0.003ml Pumilio Pine Oil and 0.78ml Squill Oxymel as the active ingredients. Other constituents are 0.125 Liquorice Liquid Extract, Anise oil, Camphor, Capsicum Tincture, Chloroform, Ethanol (96%), Diethyl Ether (Peroxide free), Linseed, Menthol, Peppermint oil, Syrup, Black treacle and purified water in each 5ml dose.

The appearance of the mixture is that of a dark brown liquid, free from particulate contamination. The odour is characteristic of Chloroform, Liquorice and Menthol from the Pumilio Pine Oil.

Coltsfoot (*Tussilaginiflos*) is an expectorant, antitussive, demulcent and anticatarrhal and is recommended in the British Herbal Pharmacopoeia for the treatment of chronic spasmodic bronchial cough.

Pumilio Pine Oil is a colourless or faintly yellow oil with a pleasant aromatic odour and bitter pungent taste obtained by distillation from the fresh leaves of *Pinus mugo* var. *Pumilio* (Pinaceae). It is recommended in Martindale The Extra Pharmacopoeia (28th Edition) page 682, to relieve cough and nasal congestion in combination with other substances and for the purposes of this submission may be treated as a flavouring. Pumilio Pine Oil is closely related to Colophony and the Terpene content of the Pine oil includes Menthol. Similar oleaceous extracts are referenced on pages 218 and 219 of the British Herbal Pharmacopoeia. It is noted that Colophony is a potent skin sensitizer and contact dermatitis may occur (see Adverse Reactions Section 3.2).



1 Introduction (cont)

Ipecacuanha is derived from plants native to Central America, but it is also cultivated in India and Malaysia. Ipecacuanha contains the Isoquinoline alkaloids (Emetine^{6,7}, Cephaeline^{6,7}, Psychotrine and Methylopsychotrine) together with Ipecacuanhic acid, Ipecacuanhin, a Saponin and Starch. It is produced from the dried root or rhizome and root of *Cephaelis ipecacuanha*.

Its therapeutic properties were known as long ago as 1658. In 1912 Vedder demonstrated in-vitro efficacy of Emetine against *E histolytica* and suggested that it might be useful to treat amoebic infections. It is prepared into a finely powdered form and adjusted with Ipecacuanha of a lower alkaloid strength. With its expectorant⁵, diaphoretic⁵ and emetic actions^{1,2,3,4,7,8,12} it has been used for bronchitis, pertussis, laryngismus, stridulus and amoebic dysentery.

Squill (*Urginea*) is the dried bulb of the *Urginea maritima* ("sea onion")¹² which is indigenous to the Mediterranean region¹¹. *Urginea* is a cream white powder and very hygroscopic. It contains cardiac glycosides of the bufadienolide type, Scillarin A¹¹ and Scillarin B.¹¹ Scillarin A, is a pure crystalline glycoside which, on hydrolysis, produces Scillaridin A together with the sugar Scillabiose. Scillarin B is a mixture of glycosides.

Squill has an irritant effect on the gastric mucosa and has been used for its reflex expectorant actions and for the treatment of chronic bronchitis¹², asthma with bronchitis¹² and whooping cough.

Prior to writing this expert report a five year retrospective search of the literature was conducted on the main active ingredients. This has produced a few papers. In addition two older papers on Squill have also been included^{11,12}. The adverse effects of both Pine balsams (Colophony) and Liquorice have been included in this report.

No expert report on the pharmacology and toxicology accompanies this submission.

2 Human pharmacology

2.1 Pharmacodynamics

Squill is used for its reflex expectorant action. Liquorice acts as a demulcent and expectorant, Coltsfoot liquid extract has also been used as a demulcent. Ipecacuanha, in small doses, has a reflex expectorant action useful for the treatment of the symptoms of acute and chronic Bronchitis, and in cough when secretion is scanty.

The two principal alkaloids of Ipecacuanha are Emetine and Cephaeline¹ of which both are amoebicidal but Emetine is much more active and constitutes more than one half of the total alkaloid content of Ipecacuanha and has a strong toxic effect on cardiac muscles. However, except for the heart, Cephaeline is much more toxic than Emetine.

In addition to its expectorant action, Squill has a cardiac action similar to Digitalis¹¹ and 800 ug given intravenously is reported to have equivalent action to 900 ug of Digoxin. Squill Oxymel¹² contains about 5% of Squill in Acetic acid, purified honey and water.

2.2 Pharmacokinetics

Several procedures have been reported for the determination of Ipecacuanha alkaloids but the classical acid-base titrimetric method would still appear to be the recommended one⁶.

2.3 Interactions

Administration with Carbenoxolone or Diuretics may cause increased toxicity of Squill if Hypokalaemia occurs.



3 Clinical documentation

3.1 Therapeutic effect

Coltsfoot, Pine and Honey Balsam is used to relieve the symptoms associated with coughs, colds and bronchitis.

Existing Ipecacuanha preparations in the United Kingdom for use as an emetic in powder and syrup form, and titrated Ipecacuanha liquid extracts, tinctures and mixtures, used in both adults and paediatric cough remedies are fully referenced in the British National Formulary BNF (1988) No 15 pages 37, 132 and 475, The Extra Pharmacopoeia, Martindale (28th Edition) pages 690 - 691 and The British Herbal Pharmacopoeia (1983) pages 57 and 58. Emetine is mentioned in Goodman and Gilman, The Pharmacological Basis of Therapeutics (7th Edition) on page 1051.

Existing Squill preparations in the United Kingdom for use in both adult and paediatric cough remedies are referenced in the British National Formulary BNF (1988) No 15 page 132, The Extra Pharmacopoeia, Martindale (28th Edition) pages 692 - 693, and The British Herbal Pharmacopoeia (1983) pages 223 - 224. Squill is also referred to on page 717 of Goodman and Gilman, The Pharmacological Basis of Therapeutics (7th Edition).

Both Ipecacuanha and Squill have expectorant and emetic actions and their combination in a cough remedy was a logical, if not scientific step. Ipecacuanha itself is mainly used for its emetic actions, both in children and adults, to prevent poisoning^{1,2,7,8,13,14} although Ipecacuanha may also mimic the effects of poisoning and its use may be inappropriate^{1,13}. Thus its usefulness has been challenged but recently favourable evidence of clinical effectiveness has emerged^{2,14}. Ipecacuanha has also been used in the recovery of drugs of abuse that have been swallowed by drug couriers⁴. Squill has been used for asthma, bronchitis and whooping cough, and in particular, when chronic bronchitis sputum is scanty. It is also used in combination with Ipecacuanha for non-productive cough in children, including whooping cough.

Coltsfoot is referenced in the Extra Pharmacopoeia, Martindale (28th Edition) page 1261 and the British Herbal Pharmacopoeia pages 220 and 221. It is not referenced in Goodman and Gilman, The Pharmaceutical Basis of Therapeutics (7th Edition) or in the British National Formulary (BNF) No 15 (1988).



3 Clinical documentation (cont)

3.1 Therapeutic effect (cont)

Pumilio Pine Oil is referenced in the Extra Pharmacopoeia, Martindale (28th Edition) page 682. It is not referenced in the British National Formulary (BNF) No 15 (1988). Similar extracts to Pumilio Pine Oil are referenced on pages 218 and 219 of the British Herbal Pharmacopoeia (1983). No references are made in Goodman and Gilman, The Pharmacological Basis of Therapeutics (7th Edition).

The recommended dose for adults and children over 12 years of age is 10ml and for children aged 5 - 12 years, 5ml. Dosage for the elderly is as for adults unless otherwise directed. The dose may be repeated after four hours if required. However, the mixture is not recommended for children under 5 years of age. None of the agents are present in their full recommended dose but their use complies with the commentary on page 132 of the BNF that the main action of such cough remedies are as placebo agents.

3.2 Adverse reactions, tolerance and interactions

Squill should not be administered to patients with impaired renal function, and is inadvisable in patients with cardiac disorders. The adverse effects of Squill include nausea and vomiting, which may also be caused by Ipecacuanha which has an irritant effect on the gastrointestinal tract. Emetine is known to accumulate in muscle and may interfere with muscle fibre contractility of heart muscle.

Ipecacuanha has caused a case of gastric rupture and death in a baby boy treated for poisoning¹⁰. Workers packing Ipecacuanha tablets were found to have a work-related allergy⁵. En passant no correlation between smoking and respiratory symptoms was found in this population.

A possible dynamic interaction has been described with a tricyclic antidepressant and Ipecacuanha⁹. Coltsfoot, Pine & Honey Balsam should be used with particular caution in children receiving compounds of this type that may have synergistic unwanted activities on the heart.

Liquorice may cause reversible Sodium retention and Potassium loss leading to hypertension, water retention and electrolyte imbalance, although the amount present in Coltsfoot, Pine and Honey Balsam makes this very remote.



3 Clinical documentation (cont)

3.2 Adverse reactions, tolerance and interactions (cont)

All drugs should be avoided if possible during the first trimester of pregnancy. Insufficient evidence is available to indicate safety of this product during pregnancy or lactation and its use is, therefore, not recommended.

It should be noted that Coltsfoot, Pine and Honey Balsam contains balsam from the sap of Pumilio Pine and other plants and products derived from the solid extracts of these sources. These extracts are essentially similar to other products (Rosin/Collophony and Collodion) that cross react with each other as potent skin sensitizers. Individual cases of sensitivity to Collophony are common⁵⁰⁻⁷⁵. Thus, the inclusion of Coltsfoot extract and Pumilio Pine extract lead to a risk of allergic reactions in sensitized individuals.

The overdose symptoms of Squill and Ipecacuanha include nausea and vomiting. The treatment of overdosage would depend upon the symptoms. Cardiac irregularities, which may be caused by Squill may be treated by emesis or aspiration and lavage. In cases of severe cardiac arrhythmias, Potassium and/or anti-arrhythmic agents may be given. Prolonged vomiting may be a symptom of overdose of Ipecacuanha alkaloids, which may be controlled by intramuscular injection of 25 to 50mg of Chlorpromazine or of a comparable dose of a related Phenothiazine; fluid and electrolyte imbalance should also be corrected.

4 Miscellaneous

This product is essentially a herbal remedy formulated to criteria more related to 19th Century medicine than to the medicine of today. The main active ingredients of this product are Ipecacuanha and Squill. The contribution of Coltsfoot is unknown and the Pine balsam should be treated as a flavouring related to, and containing terpenes, like Menthol. However, the Pine Oil does add the risk of allergy associated with Pine balsams (Colophony/Collodion) and an unquantified risk to those already sensitized. The risk of sensitisation from this preparation itself is probably remote at the dilution used in this formula. The combination is as likely as any other Ipecacuanha and Squill formulation to be effective and it may be reasonably argued that Coltsfoot, Pine Oil and Liquorice genuinely add to the overall perception of efficacy.

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4 Miscellaneous (cont)

The incidence of sensitivity to Colophony in the general population is in the range of 2% - 4%⁵⁸. Sensitivity appears to be more common in women than in men, possibly because compounds from these sources are used as excipients in perfumes and cosmetics.

Thus, the principal concern associated with Coltsfoot, Pine and Honey Balsam is that of overdose. However, both Ipecacuanha and Squill have emetic properties and vomiting is likely to be induced before significant cardiac effects, due to these two alkaloids, are detected. Appropriate warnings on use in patients with impaired renal function and cardiac disorders should appear on the label. Warning should also be included about sensitisation to Collodion/Colophony in the form of:- "Should be avoided by people allergic to Collodion/Colophony containing products eg lipsticks and eye shadows".

5 Conclusion

This expert report accompanies a submission by Thornton and Ross Ltd to continue to market Coltsfoot, Pine and Honey Balsam (Special Mixture No 233) (PLRA 0240/5209). This short review offers reassurance that Coltsfoot, Pine and Honey Balsam is a traditional remedy which remains a useful 'home' remedy when properly used and as such should remain available as a licensed medicine (but see Miscellaneous Section 4).

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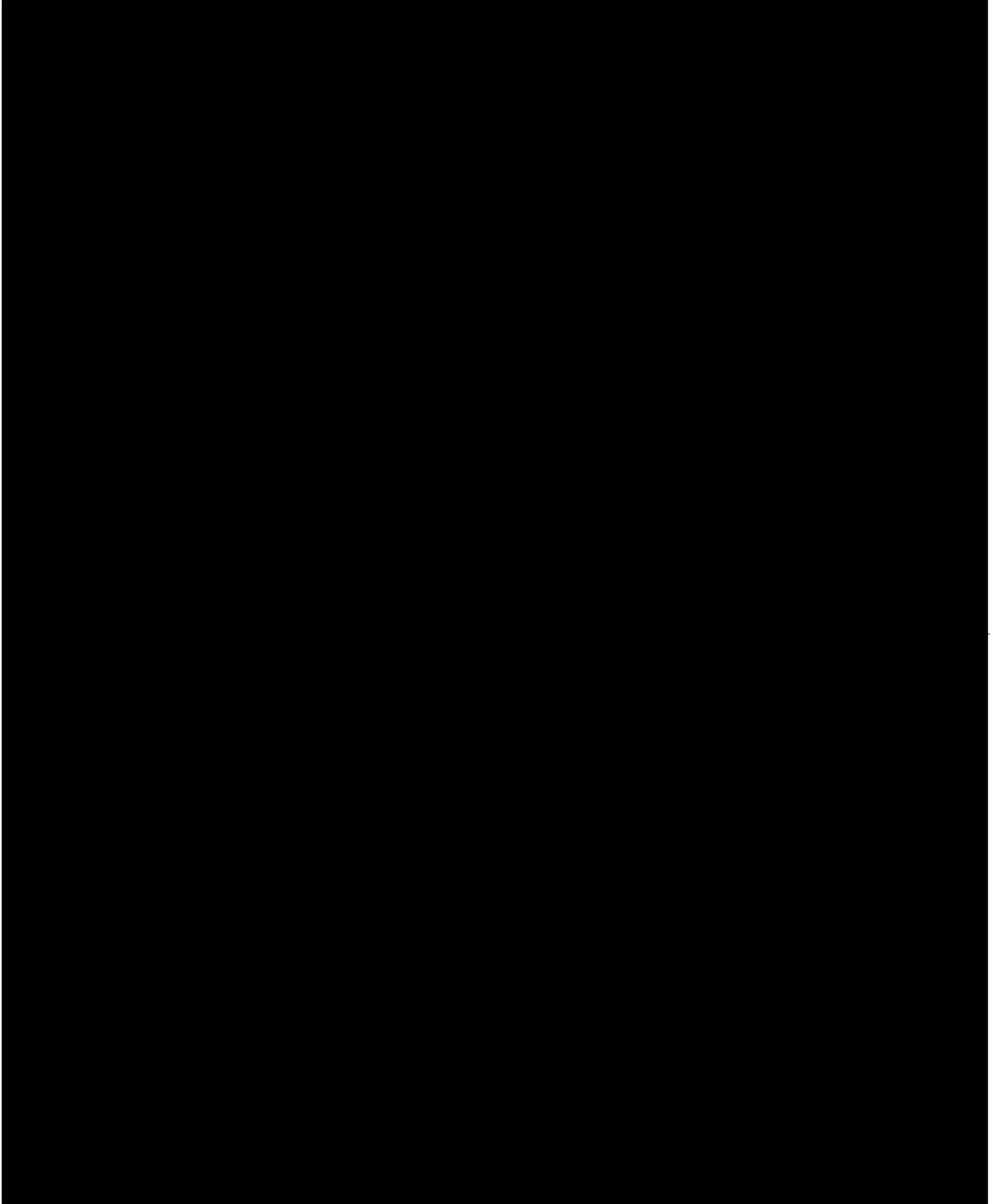
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7 Information on the expert(s)



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