

PROVISIONAL SPECIFICATION

**Antiseptic Therapeutic Compositions comprising
2:4-Dichlorobenzyl Alcohol**

We, BOOTS PURE DRUG COMPANY LIMITED, a British Company, of Station Street, Nottingham, do hereby declare this invention to be described in the following statement:—

5 This invention relates to new pharmaceutical preparations which have been found to possess valuable properties.

The invention consists in compositions which are suitable for oral or topical administration and which comprise 2:4-dichlorobenzyl alcohol in association with a pharmaceutically acceptable diluent or carrier. We have found that the compound 2:4-dichlorobenzyl alcohol possesses marked lethal activity against a wide range of bacteria and fungi and compositions containing this compound can be employed to combat bacterial and fungal infections of the ear, throat, scalp and skin. Thus the compositions of the invention include eardrops, pastilles and lozenges for medication of the throat, ointments, paints and lotions for the treatment of the skin all of which contain 2:4-dichlorobenzyl alcohol.

25 Whilst the compound 2:4-dichlorobenzyl alcohol is bactericidal and fungicidal we have also found that the value of certain of the compositions of the invention may be enhanced by the inclusion of a substance which possesses bacterostatic and fungistatic properties. A substance which is particularly valuable for this purpose is 1-methoxy-2-nitro-1-phenylethane which is effective as a bacteriostat and fungistat at very high dilutions and which is perfectly compatible with 2:4-dichlorobenzyl alcohol in the compositions of the invention. It will be understood therefore that compositions for oral or topical use which contain a combination of these two compounds form a part of the present invention.

40 The compositions of the invention which are suitable for oral use may take the form of tablets, lozenges and pastilles containing 2:4-dichlorobenzyl alcohol as active ingredient and may be prepared by methods well known in the art. The diluents which may be employed in the preparation of such compositions include those solid diluents which are non-toxic and which slowly dissolve in human saliva for example, sucrose. In addition to diluents which are incorporated for flavouring purposes it is desirable but not essential that the compositions also comprise a binding agent, for example acacia, and a minor quantity of lubricant, for example stearic acid or a metal salt thereof. The concentration of 2:4-dichlorobenzyl alcohol employed in the lozenges, etc. may vary according to the requirements of the particular medication for which they are intended. We have found that a lozenge of approximately 1 gram weight containing

5 to 20 milligrams of 2:4-dichlorobenzyl alcohol is a very convenient and valuable composition for use in medication of the throat. If desired the compositions of the invention may also contain other pharmaceutically active ingredients. Thus it has been found that the substance saligenin (*o*-hydroxybenzyl alcohol) which has local anæsthetic activity can be incorporated to give oral compositions which are particularly valuable in that they possess both bactericidal properties and local anæsthetic activity.

The compositions of the invention which are suitable for topical use include ointments, lotions, paints and eardrops containing 2:4-dichlorobenzyl alcohol as the active ingredient. Suitable ointments and creams are water-miscible or water-immiscible in character and include those of the oil-in-water emulsion and water-in-oil emulsion types which are prepared from emulsifying waxes and oils and those which are derived from water-miscible polyethylene glycols. Such ointments and creams may contain 2:4-dichlorobenzyl alcohol as the sole active ingredient or may contain a mixture of this compound and 1-methoxy-2-nitro-1-phenylethane. The ointments and creams may also comprise a small quantity of an anti-foaming agent, for example, a silicone which facilitates the application of the preparation to the skin, and a stabilising agent. A substance which is particularly suitable for use in the latter capacity is citric acid, which in addition to preventing discolouration of the ointments and creams on storage, can be used to adjust the pH of the preparation approximately to that of normal skin.

The compositions of the invention which may be employed as eardrops comprise 2:4-dichlorobenzyl alcohol in association with a relatively non-volatile liquid diluent which is innocuous when instilled into the ear. A diluent which has been found to be particularly suitable is polyethylene glycol in which 2:4-dichlorobenzyl alcohol is soluble. The eardrop compositions may include a stabilising agent, for example, citric acid to inhibit discolouration. The compositions may also comprise 1-methoxy-2-nitro-1-phenylethane if desired.

The compositions of the invention which may be employed as fungicidal and bactericidal paints and lotions comprise 2:4-dichlorobenzyl alcohol and, if desired, 1-methoxy-2-nitro-1-phenylethane in association with a liquid solvent diluent. In the case of paints the major portion of the diluent is preferably water or an aqueous alcohol which will evaporate fairly rapidly after application of the compositions to the skin, but it is prefer-

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- able to include in the composition a minor portion of a liquid of relatively low volatility for example, a polyethylene glycol, which is a solvent for the active ingredient(s) in order that the latter may be maintained in contact with the skin in the form of a concentrated solution after the bulk of the more volatile solvent has evaporated. The paint compositions are intended chiefly to be applied to feet for the treatment of bacterial and fungal infections and it is advantageous to include in the compositions a dyestuff, for example acriflavine, which will indicate where the paint has been applied. The paint compositions may also comprise one or more known fungicidal agents; for example undecylenic acid, which is commonly employed in such compositions. In the case of lotions, in particular lotions intended for application to the scalp for the treatment of dandruff, the bulk of the liquid solvent diluent is preferably a lower aliphatic alcohol, for example *isopropyl* alcohol, which may also contain a minor proportion of water. In this case also it is valuable to have present a small amount of a solvent of relatively low volatility, for example, propylene glycol in order that the active ingredient may be maintained in contact with the skin in the form of a concentrated solution. Where the lotion is intended for use as a scalp lotion by regular application to the hair, the composition may also comprise an oil, for example, *isopropyl* myristate, of the type normally employed in dressings for the hair. The compositions may also comprise other active ingredients which are commonly employed in scalp lotions, for example, hexachlorophene, salicylic acid, cetrimide etc. The concentration of 2:4-dichlorobenzyl alcohol which is employed in lotions is not critical but it has been found that a lotion containing 0.5% of this substance is efficacious in the treatment of the scalp.
- The following non-limitative examples illustrate the invention:—
- EXAMPLE 1.**
An intimate mixture of the following ingredients is compounded into lozenges each of which weighs one gram and contains 25 mgs of 2:4-dichlorobenzyl alcohol.
- | | Parts by Weight |
|----------------------------------|-----------------|
| 2:4-dichlorobenzyl alcohol - - - | 25 |
| Acacia gum - - - - - | 58 |
| Magnesium stearate - - - - | 5 |
| Sucrose to make - - - - - | 1000 |
- EXAMPLE 2.**
Lozenges each of weight 1.3 grams and of the following compositions are prepared as described below.
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|------------------------------|---------------|
| 2:4-dichlorobenzyl alcohol - | 5 milligrams |
| Saligenin - - - - - | 50 milligrams |
- Carbowax 6000 [a proprietary form of polyethylene glycol] 40 milligrams
Magnesium stearate - - - - 7 milligrams
Tragacanth - - - - - 58 milligrams
Tartaric acid - - - - - 13 milligrams
Flavouring essence - - - - 0.004 ml.
Icing sugar to make - - - - 1.3 grams
- The icing sugar and tartaric acid are thoroughly mixed and treated with a solution of the 2:4-dichlorobenzyl alcohol, saligenin and Carbowax 6000 in a small quantity of industrial methylated spirit. The product is thoroughly mixed and allowed to dry. The dried mixture is passed through a sieve of mesh 40, the tragacanth is added and mixed thoroughly before the mixture is granulated by treatment with a dilute syrup followed by drying at a temperature not exceeding 110° F. The granulated material is treated with the flavouring essence and the mixture is allowed to stand overnight in a closed container before being treated with magnesium stearate and compressed into lozenges on the appropriate machine.
- EXAMPLE 3.**
A water-miscible cream is prepared by dissolving 2 parts by weight of 2:4-dichlorobenzyl alcohol in 98 parts by weight of a polyethylene glycol 1500 available under the proprietary name of "Carbowax 1500".
- EXAMPLE 4.**
A water-miscible cream is prepared from the following ingredients by the method described below.
- | | Parts by Weight |
|---|-----------------|
| 2:4-dichlorobenzyl alcohol - - - | 1 |
| 1-methoxy-2-nitro-1-phenylethane | 0.5 |
| Polawax (a proprietary material consisting of stearyl alcohol with a non-ionic emulsifying agent) | 15 |
| Liquid paraffin - - - - - | 10 |
| Silicone fluid (M.S. 200/20) (a proprietary anti-foaming preparation) - - - - - | 0.5 |
| Polyethylene glycol 400 - - - - | 45 |
| Citric acid - - - - - | 0.2 |
| Odiferant - - - - - | 0.3 |
| Water to make - - - - - | 100 |
- A mixture of the Polawax, liquid paraffin and silicone fluid is heated to 65° C. and treated during high speed stirring, with a solution of the citric acid in a mixture of the water and half of the propylene glycol 400 previously heated to 65° C. The mixture is cooled to 40° C. and a solution of the 2:4-dichlorobenzyl alcohol and 1-methoxy-2-nitro-1-phenylethane in the remainder of the polyethylene glycol 400 is added with stirring. To the resulting product is added the odiferant and the mixture is stirred until a cream is formed.

EXAMPLE 5.

An eardrop preparation of the following composition is obtained by the process described below.

	Parts by Weight
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2:4-dichlorobenzyl alcohol - -	2.5
1-methoxy-2-nitro-1-phenylethane	2.5
Citric acid - - - - -	0.2
10 Polyethylene glycol 300 (a proprietary brand of polyethylene glycol) to make - - -	100
The 2:4-dichlorobenzyl alcohol and 1-methoxy-2-nitro-1-phenylethane are dissolved with gentle warming in a small portion of the polyethylene glycol 300 and treated with a solution of the citric acid in a small portion of the polyethylene glycol 300. The resulting mixture is then diluted with the remainder	
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20 of the polyethylene glycol 300.	

EXAMPLE 6.

A formulation suitable for use as a fungicidal and bactericidal paint and of the following composition is prepared by the process described below.

	Parts by Weight
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2:4-dichlorobenzyl alcohol - -	2.0
1-methoxy-2-nitro-1-phenylethane	0.5
30 Polyethylene glycol 400 - - -	5.0
Acriflavine - - - - -	0.05
Industrial methylated spirit - -	60
Water to make - - - - -	100
The 2:4-dichlorobenzyl alcohol and 1-methoxy-2-nitro-1-phenylethane are dissolved in the industrial methylated spirit and this solution is mixed with a solution of the acri-	
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flavine in a mixture of the polyethylene glycol 400 and a portion of the water. The volume of the resulting solution is adjusted by the addition of the remainder of the water. 40

EXAMPLE 7.

A formulation suitable for use as a scalp lotion and of the following composition is prepared by dissolving all the ingredients apart from the water in a major portion of the isopropyl alcohol, adding the water to the resulting solution with stirring and finally adding the remainder of the isopropyl alcohol.

	Parts by Weight
2:4-dichlorobenzyl alcohol - -	0.5
Hexachlorophene - - - - -	0.2
Salicylic acid - - - - -	1.0
Cholesterol - - - - -	0.2
Cetrimide B.P. - - - - -	0.5
Isopropyl myristate - - - - -	3.0
Propylene glycol - - - - -	5.0
Water - - - - -	25
Perfume - - - - -	0.8
Isopropyl alcohol to make - -	100
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EXAMPLE 8.

An oily formulation suitable for use as a scalp lotion is prepared according to the method described in Example 7, the proportion of isopropyl myristate being increased to 19.0 parts by weight and the proportion of water being reduced to 24 parts by weight. 65

For the Applicants:

GILL, JENNINGS & EVERY,
Chartered Patent Agents,
51/52, Chancery Lane, London, W.C.2.