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(54) Title: NOVEL COMPOSITIONS

(57) Abstract: This invention relates to formulations of fentanyl, especially pump spray formulations suitable for sublingual delivery.

Novel Compositions

This invention relates to formulations of fentanyl, especially pump spray formulations suitable for sublingual delivery.

Fentanyl is a narcotic alkaloid, which has been used for many years as an anaesthetic and an analgesic, especially in the treatment of moderate to severe pain. Whilst undoubtedly effective for pain relief, and especially in the treatment of pain which is refractive to other treatments, there are a number of issues of clinical management associated with the use of fentanyl in therapy.

Foremost amongst these issues is the potential for serious side effects with fentanyl. It has a much higher potency than commonly known narcotics and therefore it is necessary to ensure that it is being used within the established therapeutically effective range and to monitor patients for evidence of self medication at greater than the recommended amount. Overdosage with fentanyl can lead to a number of undesirable and indeed life-threatening side effects, predominantly hypoventilation and respiratory depression.

Due to the nature of the conditions being treated, it is much desired that the onset of analgesia occurs as soon after dosage as is compatible with safety parameters. Furthermore delay in onset of action may prompt the patient to take another dose with consequent risk, as already explained above, of overdosage.

A number of routes of administration of a medicament can be associated with rapid onset of action. For example, International Patent Application WO90/07333 (Riker Labs) described aerosol formulations of fentanyl, which are adapted for inhalation. However Riker's formulations suffer disadvantages such as their use of hydrofluorocarbon propellants and delivery effected by metered dose inhalers. In the case of the former the disadvantages include high velocity which results in 'bounce back' on administration to the front of the mouth, cold sensations on administration, the risk of inhalation and for the latter, careful co-ordination of

breath and actuation by the patient. When metered dose inhalers are used, a significant proportion of the delivered dose tends to impact the back of the throat from where it is swallowed rather than finding its way into the bronchial passages. Accordingly, the pharmacology of the medication may be unpredictable due to poor bioavailability following oral administration or may be characterised by a bi-phasic profile (fast initial onset as a result of the inhaled dose and a slower, late effect due to oral absorption of fentanyl). Furthermore, manufacture of the bulk formulation involves the preparation of large quantities of pressurised volatile propellant containing a potent narcotic analgesic. Accordingly the precautions required to ensure safe manufacture are onerous and expensive.

WO95/31182 (Aradigm Corp) describes solution formulations of fentanyl in aerosol propellants intended for administration to patients by the pulmonary route.

WO01/97780 (Pharmasol Ltd) describes solution formulations of fentanyl free base in propellants, typically HFA134a, for sublingual aerosol administration.

WO00/47203 (MQS Inc) describes formulations of fentanyl citrate for intra-oral administration employing oral absorption enhancers.

These prior art formulations of fentanyl employ propellants and also suffer from the aforementioned disadvantages.

Certain aqueous formulations of fentanyl for intranasal administration employing water and phosphate buffer have been described, (Paech, M.J., Lim, C.B., Banks, S.L., Rucklidge, M. W. M. & Doherty, D.A. (2003) Anaesthesia 58 (8), 740-744 and Lim et al (2003) J Pharm Practice Research 33, 59-63) but such formulations can suffer problems of nasal irritation associated with medium to long term usage via this route which is undesirable. Weinberg et al (1988) Clin Pharmacol Therap 44 335-342 discloses formulations of fentanyl employing water and phosphate buffer for sublingual administration however these formulations were not advocated for use as a spray.

It is well known that the application of carefully chosen medicaments to the sublingual mucosa offers a route of administration which is capable of resulting in very rapid transmission of medicament to the bloodstream with consequent fast onset of effect. A number of ways of administering compositions sublingually are known. For example, tablets or liquids may be held under the tongue prior to swallowing. Another method is spray delivery. Of these various types of sublingual administration, spray delivery is preferred as it does not involve holding the composition under the tongue for an extended period of time as, for example, with a lozenge and it reduces the amount of material which is swallowed (and may enter the blood stream in a delayed manner via the gastrointestinal tract). Pharmaceutical compositions, for example a fentanyl lozenge cause increased salivation, which facilitates the unwanted swallowing of drug substance. Spray delivery, having low volume and ability to target the sublingual mucosa, largely mitigates this. No propellant free spray formulations of fentanyl which are adapted for sublingual administration have yet been described.

It is an aim of the present invention to provide a formulation, which avoids or mitigates some or all of the above-mentioned disadvantages.

Thus according to a first aspect of the invention a pharmaceutical composition is provided, the composition being a partially pressurised liquid spray formulation, which comprises:

(a) fentanyl or a pharmaceutically acceptable salt thereof;

(b) water as carrier; and

(c) a polar organic solvent in sufficient amount to enhance the solubility of the fentanyl or pharmaceutically acceptable salt thereof in the water.

The formulations of the invention are preferably administered sublingually as a spray. The formulations are well tolerated when administered to the sensitive sublingual mucosa and the sublingual spray administration will result in rapid onset of the therapeutic effect of the fentanyl.

The formulations of the present invention are also preferably free of any propellant.

Amongst the advantages of these formulations is the fact that by being water based they avoid the issues associated with using pressurised hydrofluorocarbon propellants as mentioned above. The formulations are partially pressurised and are free of propellants such as volatile chlorofluorocarbons (e.g. propellant 12), volatile hydrofluoroalkanes (e.g. 1,1,1,2-tetrafluoroethane and 1,1,1,2,3,3,3-heptafluoro-n-propane) and volatile alkanes (e.g. propane, butane) and other substances which have significant vapour pressure at ambient temperature and pressure.

In one embodiment of the present invention, the formulation is a solution, rather than a suspension. Whilst it is possible to spray a suspension, the fact that most suspensions settle means that the amount of active agent included in the dispensed dose will be variable and this can be highly undesirable. Although the effect of the settling of the suspension can be reduced to an extent by shaking the composition prior to spraying, some suspensions can settle very rapidly, so that there is still potential for variation of active agent content between doses.

Furthermore the formulations of the present invention are characterised by good long-term physical and chemical stability.

Fentanyl may be employed in the form of a physiologically acceptable salt, which is soluble in water together with a polar organic solvent. Examples of suitable salts include hydrochloride, chloride, sulphate, tartrate and citrate. Preferably fentanyl is employed as the free base.

Preferably the fentanyl or physiologically acceptable salt thereof will be employed in the formulation at a concentration of 0.1mg/ml to 10mg/ml, preferably 0.5mg/ml to 4.4mg/ml (where weight is expressed as weight of fentanyl free base).

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