efficacy study of nalmefene, as-needed use, in patients with alcohol dependence. *European Neuropsychopharmacology* (2013); 23(11): 1432-1442; van den Brink et al., Long-term efficacy, tolerability and safety of nalmefene as-needed in patients with alcohol dependence: A 1-year, randomised controlled study. *J. Psychopharmacol.*, published online before print March 26, 2014, doi: 10.1177/0269881114527362) and 5 studies in alcohol use disorders conducted by the company Biotie (Karhuvaara et al. *Alcohol. Clin Exp Res.* (2007); 31: 1179-1187).

A marketing authorization was granted in February 2013 in the European Union (EU) for oral nalmefene under the tradename Selincro® for the reduction of alcohol consumption in adult patients with alcohol dependence.

The only known salt of nalmefene is the hydrochloride salt. Said nalmefene hydrochloride salt has been described as a hydrate-forming salt and known forms are nalmefene hydrochloride monohydrate (Brittain, H.G., *Analytical Profiles of Drug Substances and Excipients*; 1996, Vol. 24: 351-395) and nalmefene hydrochloride dihydrate (WO 2010/063292). Methods for obtaining said nalmefene hydrochloride monohydrate and dihydrate from crude nalmefene hydrochloride are described in WO 2010/063292.

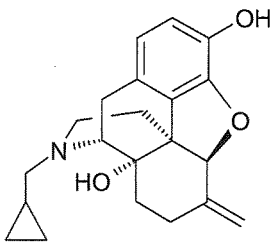
It has not been possible to obtain a stable anhydrous form of Nalmefene hydrochloride as formation of anhydrous material by dehydration of a hydrate lead to hygroscopic material that absorbs water under transformation to a hydrate, and crystallization from ethanol lead to ethanol solvate (Brittain, H.G., *Analytical Profiles of Drug Substances and Excipients*; 1996, Vol. 24: 351-395 and WO 2010/063292).

There is a need for new salts of nalmefene with improved properties e.g. for chemical processing and for pharmaceutical formulation and storage.

SUMMARY OF THE INVENTION

The ~~invention~~ disclosure provides new nalmefene salts which possess at least one of the following properties: non-solvate forming and non-hydrate forming.

In one aspect, ~~T~~the present invention relates to a salt of the compound of formula [I]



[I]

wherein said salt falls within at least one of the two following categories:

a) non-hydrate forming salt;

b) non-solvate forming salt.

In ~~one embodiment~~another aspect, the invention relates to a pharmaceutical composition comprising a salt of the present invention.

In ~~one embodiment~~a further aspect, the invention relates to a salt of the present invention for use in therapy.

In ~~one embodiment~~ yet another aspect, the invention relates to a use of the salt or the pharmaceutical composition of the present invention in the manufacture of a medicament, for ~~use in~~ reduction of alcohol consumption in a patient with alcohol dependence.

BRIEF DESCRIPTION OF DRAWINGS

X-ray powder diffractograms (XRPDs) according to figures 1-8 are obtained using $CuK_{\alpha 1}$ radiation (λ=1.5406 Å). The y-axis shows the intensity (counts) and the x-axis shows the 2θ-angles (°).

Figure 1: XRPD pattern of the hydrogen adipate salt of nalmefene.

Figure 2: XRPD pattern of the hydrogen malonate salt of nalmefene.

Figure 3: XRPD pattern of the L-lactate salt of nalmefene.

Figure 4: XRPD pattern of the hydrogen fumarate salt of nalmefene.

Figure 5: XRPD pattern of the hydrogen succinate salt of nalmefene.

Figure 6: XRPD pattern of the benzene sulfonate salt of nalmefene.

Figure 7: XRPD pattern of the hydrogen maleate salt of nalmefene.

Figure 8: XRPD pattern of the salicylate salt of nalmefene.

TGA and DSC profiles of nalmefene salts are shown in Figures 9-16. The X axis shows the temperature (°C), the left hand y-axis shows the TGA weight loss (%), the right hand y-axis shows the DSC heat flow (W/g).

Figure 9: TGA and DSC thermograms of the hydrogen adipate salt of nalmefene.

Figure 10: TGA and DSC thermograms of the hydrogen malonate salt of nalmefene.

Figure 11: TGA and DSC thermograms of the L-lactate salt of nalmefene.

Figure 12: TGA and DSC thermograms of the hydrogen fumarate salt of nalmefene.

Figure 13: TGA and DSC thermograms of the hydrogen succinate salt of nalmefene.

Figure 14: TGA and DSC thermograms of the benzene sulfonate salt of nalmefene.

Figure 15: TGA and DSC thermograms of the hydrogen maleate salt of nalmefene.

Figure 16: TGA and DSC thermograms of the salicylate salt of nalmefene.

Figure 17: Table with structural formulas of [a]: adipic acid, [b]: malonic acid, [c]: lactic acid, [d]: fumaric acid, [e]: succinic acid, [f]: benzene sulfonic acid, [g]: maleic acid, [h]: salicylic acid.

9. The salt according to claim 8, which salt does not form solvate when precipitated from any of the solvents selected from EtOH, MeOH, IPA, EtOAc, acetone, ACN, THF, MIBK, toluene and 2,2,2-trifluoroethanol.

10. The salt according to any of claims 1-3, which salt when precipitated from one of the solvents selected from EtOH, MeOH, IPA, EtOAc, acetone, ACN, THF, MIBK, toluene and 2,2,2-trifluoroethanol, does only form solvate from one or two of said solvents.

11. The salt according to any of claims 1-9, wherein said salt is both a non-hydrate forming salt and a non-solvate forming salt.

12. A pharmaceutical composition comprising a salt according to any of claims 1-11.

13. The pharmaceutical composition according to claim 12, characterized in that said composition are manufactured by a process comprising one or more of the process steps selected from wet granulation, fluid bed processing, drying at elevated temperature such as at a temperature above room temperature, aqueous based spray drying, aqueous based coating of granules, pellets or tablets, milling at elevated temperature.

14. A salt according to any of claims 1-11 for use in therapy.

15. Use of ~~A~~a salt according to any of claims 1-11 or a pharmaceutical composition according to any of claims 12-13 in the manufacture of a medicament, for ~~use~~ reduction of alcohol consumption in a patient with alcohol dependence.