product was isolated by extraction in water at acidic pHs and then precipitating at basic pHs giving nalmefene as base.

Even though the isolation procedure for nalmefene as free base is simplified, it still has some disadvantages. The inventors of the present invention repeated the method disclosed in US 4,751,307 and found that the removal of phosphine oxide by-products was not efficient. These impurities co-precipitate with the nalmefene during basification, yielding a product still contaminated with phosphorus by-products and having, as a consequence, a low chemical purity, as illustrated in example 2 herein.

There is therefore a need within the field to improve the method of producing nalmefene by the Wittig reaction. In particular, there is a need for a method that is readily applicable on a large industrial scale and which avoids the use of water-miscible solvents, such as THF, in the Wittig reaction, and permits easy isolation of nalmefene in a pure form suitable for its transformation to the final pharmaceutical salt form.

The inventors of the present invention have met this goal by developing an improved method for the preparation of nalmefene which is applicable on an industrial scale and results in a highly pure nalmefene as the hydrochloride salt.

Summary ~~of the invention~~

The present invention relates to a method for preparing nalmefene from naltrexone in a Wittig reaction wherein 2-methyltetrahydrofuran (MTHF) is used both in the formation of a phosphorus ylide and in the subsequent reaction between the ylide and naltrexone.

In one embodiment~~a further aspect~~, the disclosure provides~~invention also relates to~~ a pharmaceutical composition comprising the nalmefene hydrochloride obtained by the method described herein.