Specific dosage or administration forms of selected salts or crystalline forms of IM-250 have not yet been described.

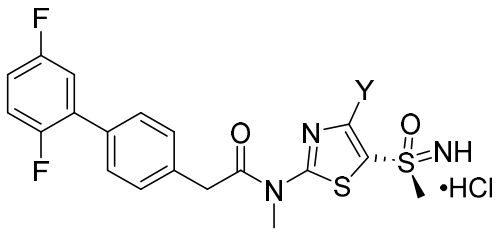
The scientific publication of *Serajuddin A. T. M. "Salt formation to improve drug solubility", Adv. Drug Deliv. Rev. 2007; 59:603-616* discloses the relationship between salt formation of pharmaceutically active species and its influence on solubility, dissolution rate and related factors in the context of drug bioavailability.

Kesisoglu et al. "Understanding the Effect of ApI Properties on Bioavailability Through Absorption Modeling", The AAPS Journal, 2008; 10(4):516-525 describes solid phase and physical properties of active pharmaceutical ingredients and how the particle size of a pharmaceutical ingredient may influence its absorption properties and ultimately the drug bioavailability.

Crystallisation or salt formation may positively influence important drug properties, such as solubility, dissolution rate, bioavailability, hygroscopicity, flavor, developability and physical/chemical stability. There is a need to provide optimized dosage or administration forms of antiviral compounds according Formula (A), which exhibit optimized physicochemical and pharmaceutical properties, without affecting negatively other important parameters, such as hygroscopicity or bioavailability of the active compound with the final goal to obtain an improvement in the production, handling, storage and pharmaceutical properties of said compounds according Formula (A).

SUMMARY

The present invention relates to novel, selected crystalline forms of the hydrochloride salt of the antiviral helicase-primase inhibitor **IM-250** with Formula (**I**) in micronized form:

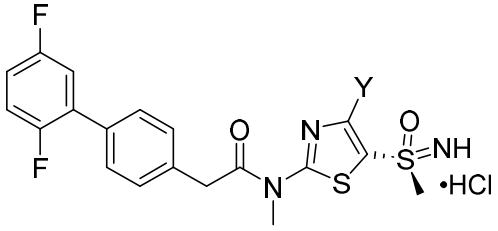


Formula (**I**)

,

wherein Y is selected from CH_3 or CD_3, or a co-crystal, hydrate or solvate thereof.

In one aspect, the present disclosure provides a micronized, crystalline form of a compound according to Formula (**I**)



Formula (**I**)

wherein Y is selected from CH_3 and CD_3;

or a co-crystal, hydrate or solvate thereof, wherein the micronized crystalline form is characterized by a particle size (d_{90} value / d_{90} particle size distribution), which is reduced by a factor of at least 10 compared to the non-micronized form.

In another aspect, the present disclosure provides a pharmaceutical composition comprising a therapeutically effective amount of a micronized, crystalline form of Formula (**I**) as described herein, and at least one pharmaceutically acceptable carrier and/or excipient and/or at least one further active substance being effective in treating a disease or disorder associated with viral infections (antiviral active compounds).

These novel selected micronized crystalline forms are useful, for example, for treating human patients suffering from a herpes simplex-mediated disorder. The novel micronized solid forms of the present disclosure can be useful for preparing a medicament for treating or preventing herpes simplex virus infections and disease. The novel micronized solid forms of the present disclosure can be used as helicase-primase inhibitors. The inventors of the present invention surprisingly found that providing the selected crystalline hydrochloride salt forms of **IM-250** in micronized form further improves their suitability for providing medicaments with optimized properties, such advantages comprise, for example, allowing administration at a lower dose compared to the non-micronized matched pair due to improved bioavailability. Therewith, the

inventors of the present invention for the first time combined the particular advantages having been shown for the selected **IM-250 HCl salt form** and its deuterated analog with the advantages of providing the drug in micronized form to offer a new and improved **IM-250** dosage or administration form.

In a further aspect, the present disclosure provides the micronized, crystalline forms as described herein, or the pharmaceutical composition described herein for use in the prophylaxis and treatment of a herpes simplex infection or -mediated disorder, including the treatment or elimination of latent forms of herpes viruses in neuronal tissue and nerves, and including prevention and treatment of recurrence and reactivation of herpes infections or severe implications associated therewith, such as herpes simplex encephalitis (HSE).

DESCRIPTION OF FIGURES

Figure 1 depicts a X-ray powder diffraction (XRPD) pattern of **IM-250 HCl salt**.

Figure 2 depicts a XRPD pattern of **IM-250 HCl salt** when crystallized from EtOH.

Figure 3 depicts a XRPD pattern of **deuterated IM-250 HCl salt (d_3-IM-250 HCl salt)**.

Figure 4 microscopy observation of **IM-250 HCl salt** crystals for PSD assessment in transmitted light and cross-polarized light – magnifications x162.

Figure 5 microscopy observation of **IM-250 HCl salt** crystals (same crystals as in Figure 4) in cross-polarized light – magnifications x162.

Figure 6 granulometric profile of **IM-250 HCl salt** crystals (cumulated particle size distribution).

Figure 7 distribution histogram of **IM-250 HCl salt** PSD assessment.

Figure 8 particle size distribution by laser diffraction of micronized **IM-250 HCl salt**.

Figure 9 microscopy observation of micronized **IM-250 HCl salt**.

Figure 10 overlaid XRPD profiles for the native **IM-250 HCl salt** batch and the same batch after micronization.

Figure 11 overlaid DSC profiles for the native **IM-250 HCl salt** batch and the same batch after micronization.

Figure 12 microscopy observation of **d_3-IM-250 HCl salt** crystals for PSD assessment in transmitted light and cross-polarized light – magnifications x162.

Figure 13 microscopy observation of **d_3-IM-250 HCl salt** crystals (same crystals as in Figure 4) in cross-polarized light – magnifications x162.

Figure 14 granulometric profile of **d_3-IM-250 HCl salt** crystals (cumulated particle size distribution).

Figure 15 distribution histogram of **d_3-IM-250 HCl salt** PSD assessment.

Figure 16 particle size distribution by laser diffraction of micronized **d_3-IM-250 HCl salt**.

Figure 17 microscopy observation of micronized **d_3-IM-250 HCl salt**.

Figure 18 particle size distribution by laser diffraction and d_{90} value of **IM-250 HCl salt** (GMP-campaign) before micronization.

Figure 19 particle size distribution by laser diffraction and d_{90} value of micronized **IM-250 HCl salt** (GMP-campaign).