
From: Santos, Ivan [/O=MERCK/OU=NORTHAMERICA/CN=RECIPIENTS/CN=SANTOSIV]
Sent: 2/23/2002 10:42:28 AM
To: Ostovic, Drazen [drazen_ostovic@merck.com]; Shultz, Leigh [Shulleig@NorthAmerica.msx.merck.com]; Remenar, Julius F. [remenarj@NorthAmerica.msx.merck.com]; Armstrong, Joe D [joe_armstrong@merck.com]; Palucki, Michael [michael_palucki@merck.com]; Hansen, Karl [karl_hansen@merck.com]; Lindemann, Christopher M [christopher_lindemann@merck.com]; Zhang, Dina [dina_zhang@merck.com]; Hurter, Patricia N [patricia_hurter@merck.com]; Thornberry, Nancy A [nancy_thornberry@merck.com]
CC: Luna, Ernestina A. [ernestina_luna@merck.com]; Liu, Yun [yun_liu@merck.com]; Kube, Kenneth P [kenneth_kube@merck.com]; Gandek, Thomas P. [thomas_gandek@merck.com]; Boyle Briggs, Kelly A [kelly_boylebriggs@merck.com]; Egan, Richard S. [richard_egan@merck.com]; Thomas, Scott M [scott_thomas@merck.com]
Subject: RE: Salt selection for L-224715

I too recommend the phosphate salt. Given the data we have to date we have a simple solid state system, good solubility and stability, a workable morphology, this is incredible not often do we see these, I hope the secondary processing goes well and or coarse we will continue to keep an eye on the API during scale up.

-----Original Message-----

From: Ostovic, Drazen
Sent: Thursday, February 21, 2002 1:17 PM
To: Shultz, Leigh; Remenar, Julius F.; Armstrong, Joe D; Palucki, Michael; Hansen, Karl; Santos, Ivan; Lindemann, Christopher M; Zhang, Dina; Hurter, Patricia N; Thornberry, Nancy A
Cc: Luna, Ernestina A.; Liu, Yun; Kube, Kenneth P; Gandek, Thomas P.; Boyle Briggs, Kelly A
Subject: RE: Salt selection for L-224715

I second Leigh's recommendation. The data speak.
Drazen

-----Original Message-----

From: Shultz, Leigh
Sent: Thursday, February 21, 2002 1:12 PM
To: Remenar, Julius F.; Ostovic, Drazen; Armstrong, Joe D; Palucki, Michael; Hansen, Karl; Santos, Ivan; Lindemann, Christopher M; Zhang, Dina; Hurter, Patricia N; Thornberry, Nancy A
Cc: Luna, Ernestina A.; Liu, Yun; Kube, Kenneth P; Gandek, Thomas P.; Boyle Briggs, Kelly A
Subject: Salt selection for L-224715

Everyone,

Two-week stability data is now available for the phosphate salt of L-224715. It shows no stability problems in the bulk after 2 weeks at 40/75 and 80 C (this is true for all the salts of 715). In water, it is the most stable of the three salts toward both hydrolysis and de-amination. Comparative stability data for the three salts and the free base are shown below:

<< OLE Object: Picture (Metafile) >>

Note that 4-week data for the besylate salt (new) confirms that the stability of this salt in water is not appreciably better than the stability of the free base. Only one polymorph has been observed for the phosphate salt to date, and no hydrates have been found (Chris, please add anything new you may have found here). The salt is non-hygroscopic but freely soluble in water (>100 mg/mL salt, >80 mg/mL 715). It has low solubility in possible granulating solvents such as ethanol and 2-propanol (<0.1 mg/mL free base), and no evidence for amorphous material in the solubility samples was observed by microscopy. Although the salt has high water solubility, no deliquescence was observed after storage of the bulk at 40 C/75% RH for one week. The flake-like morphology of this salt is preferable to the needles and rods seen with the besylate and tartrate. Based on this data, I recommend selecting the phosphate salt of L-224715 for Phase I development and Safety Assessment studies.

Leigh

Leigh Shultz, PhD
Senior Research Chemist
Pharmaceutical R&D
Mail Stop: RY80M-112
Tel: 782 524 1117

