from the enterohepatic circulation leads to a decrease in the level of bile acids in serum and the liver. Odevixibat, or a pharmaceutically acceptable salt thereof, is therefore useful in the treatment or prevention of diseases such as dyslipidemia, constipation, diabetes and liver diseases, and especially liver diseases that are associated with elevated bile acid levels.

According to the experimental section of WO 03/022286, the last step in the preparation of odevixibat involves the hydrolysis of a tert-butyl ester under acidic conditions. The crude compound was obtained by evaporation of the solvent under reduced pressure followed by purification of the residue by preparative HPLC (Example 29). No crystalline material was identified.

Amorphous materials may contain high levels of residual solvents, which is highly undesirable for materials that should be used as pharmaceuticals. Also, because of their lower chemical and physical stability, as compared with crystalline material, amorphous materials may display faster decomposition and may spontaneously form crystals with a variable degree of crystallinity. This may result in unreproducible solubility rates and difficulties in storing and handling the material. In pharmaceutical preparations, the active pharmaceutical ingredient (API) is for that reason preferably used in a highly crystalline state. Thus, there is a need for crystal modifications of odevixibat having improved properties with respect to stability, bulk handling and solubility. In particular, it is an object of the present invention to provide a stable crystal modification of odevixibat that does not contain high levels of residual solvents, that has improved chemical stability and can be obtained in high levels of crystallinity.

SUMMARY

The disclosure provides crystal modifications of odevixibat. In a first example, the crystal modification is a crystalline hydrate of odevixibat. This crystalline hydrate is a channel hydrate, which may contain up to 2 moles of water associated with the crystal per mole of odevixibat. The amount of water calculated herein excludes water adsorbed to the surface of the crystal. In one example, the crystalline hydrate is a sesquihydrate, *i.e.*, contains about 1.5 moles of water associated with the crystal per mole of odevixibat. In another example, which may be related to the first aspect, the disclosure provides crystal modification 1 of odevixibat. Crystal modification 1 is a stable crystalline hydrate which at 30% relative humidity (RH) contains about 1.5 moles of water per mole of odevixibat.

In another aspect, the present disclosure refers to crystal modification 1 of odevixibat, having an XRPD pattern, obtained with CuKα1-radiation, with peaks at °2θ positions 5.6 ± 0.2, 6.7 ± 0.2 and 12.1 ± 0.2. In yet another example, the present disclosure refers to a mixed solvate of odevixibat, containing about two moles of water per mole of odevixibat. In yet another aspect, the present disclosure refers to crystal modification 2A of odevixibat, having an XRPD pattern, obtained with CuKα1-radiation, with peaks at °2θ positions 5.0 ± 0.2, 5.1 ± 0.2 and 11.8 ± 0.2. In yet another aspect, the present disclosure refers to crystal modification 2B of odevixibat, having an XRPD pattern, obtained with CuKα1-radiation, with peaks at °2θ positions 4.8 ± 0.2, 5.1 ± 0.2 and 11.6 ± 0.2. In yet another aspect, the present disclosure refers to crystal modification 2C of odevixibat, having an XRPD pattern, obtained with CuKα1-radiation, with peaks at °2θ positions 5.0 ± 0.2, 6.2 ± 0.2, 9.4 ± 0.2 and 23.9 ± 0.2. In yet another aspect, the present disclosure refers to use of crystal modification 2A, 2B or 2C of odevixibat as described herein in a process for the preparation of crystal modification 1 of odevixibat as described herein.

In a further aspect, the present disclosure refers to a process for the preparation of crystal modification 1 of odevixibat as described herein, comprising isolating crystal modification 2A, 2B or 2C of odevixibat as described herein from a solution of odevixibat in a solvent mixture comprising water and an organic solvent selected from the group consisting of methanol, ethanol, 2-propanol, acetone, acetonitrile, 1,4-dioxane, DMF and DMSO. In a further aspect, the present disclosure refers to a pharmaceutical composition comprising crystal modification 1 of odevixibat as described herein, together with a pharmaceutically acceptable diluent or carrier. In a further aspect, the present disclosure refers to crystal modification 1 of odevixibat as described herein, for use in therapy. In a further aspect, the present disclosure refers to use of crystal modification 1 of odevixibat as described herein in the manufacture of a medicament for the treatment or prevention of a cardiovascular disease or a disorder of fatty acid metabolism or a glucose utilization disorder, such as hypercholesterolemia; disorders of fatty acid metabolism; type 1 and type 2 diabetes mellitus; complications of diabetes, including cataracts, micro- and macrovascular diseases, retinopathy, neuropathy, nephropathy and delayed wound healing, tissue ischaemia, diabetic foot, arteriosclerosis, myocardial infarction, acute coronary syndrome, unstable angina pectoris, stable angina pectoris, stroke, peripheral arterial occlusive disease, cardiomyopathy, heart failure, heart rhythm disorders and vascular restenosis; diabetes-related diseases such as insulin resistance (impaired glucose homeostasis), hyperglycemia, hyperinsulinemia, elevated blood levels of fatty acids or glycerol, obesity, dyslipidemia, hyperlipidemia including hypertriglyceridemia, metabolic syndrome (syndrome X), atherosclerosis and hypertension; and for increasing high density lipoprotein levels.

CLAIMS

1. Crystal modification 1 of odevixibat, having an XRPD pattern, obtained with CuKα1-radiation, with peaks at °2θ positions 5.6 ± 0.2, 6.7 ± 0.2 and 12.1 ± 0.2.

2. The crystal modification according to claim 1, having an XRPD pattern, obtained with CuKα1-radiation, with specific peaks at °2θ positions 5.6 ± 0.2, 6.7 ± 0.2 and 12.1 ± 0.2 and one or more of the characteristic peaks: 4.1 ± 0.2, 4.6 ± 0.2, 9.3 ± 0.2, 9.4 ± 0.2 and 10.7 ± 0.2.

3. Crystal modification 1 of odevixibat according to claim 1, having an XRPD pattern, obtained with CuKα1-radiation, as shown in FIG. 1.

4. Crystal modification 1 of odevixibat according to any one of claims 1 to 3, having a crystallinity of greater than about 99%.

5. Crystal modification 2A of odevixibat, having an XRPD pattern, obtained with CuKα1-radiation, with peaks at °2θ positions 5.0 ± 0.2, 5.1 ± 0.2 and 11.8 ± 0.2.

6. The crystal modification according to claim 5, having an XRPD pattern, obtained with CuKα1-radiation, with peaks at °2θ positions 5.0 ± 0.2, 5.1 ± 0.2, 6.4 ± 0.2, 6.6 ± 0.2, 9.5 ± 0.2 and 11.8 ± 0.2.

7. Crystal modification 2A of odevixibat according to claim 5, having an XRPD pattern, obtained with CuKα1-radiation, as shown in any one of FIG. 6 to 9.

8. Crystal modification 2B of odevixibat, having an XRPD pattern, obtained with CuKα1-radiation, with peaks at °2θ positions 4.8 ± 0.2, 5.1 ± 0.2 and 11.6 ± 0.2.

9. The crystal modification according to claim 8, having an XRPD pattern, obtained with CuKα1-radiation, with peaks at °2θ positions 4.8 ± 0.2, 5.1 ± 0.2, 6.2 ± 0.2, 6.67 ± 0.2, 9.5 ± 0.2, 11.6 ± 0.2 and 20.3 ± 0.

10. Crystal modification 2B of odevixibat according to claim 8, having an XRPD pattern, obtained with CuKα1-radiation, as shown in FIG. 10 or 11.

11. Crystal modification 2C of odevixibat, having an XRPD pattern, obtained with CuKα1-radiation, with peaks at °2θ positions 5.0 ± 0.2, 6.2 ± 0.2, 9.4 ± 0.2 and 23.9 ± 0.2.

12. The crystal modification according to claim 11, having an XRPD pattern, obtained with CuKα1-radiation, with peaks at °2θ positions 5.0 ± 0.2, 6.2 ± 0.2, 9.4 ± 0.2 and 23.9 ± 0.2 and one or more of the characteristic peaks: 11.5 ± 0.2, 19.5 ± 0.2 and 20.2 ± 0.2.

13. Crystal modification 2C of odevixibat according to claim 11, having an XRPD pattern, obtained with CuKα1-radiation, as shown in FIG. 12.

14. Use of crystal modification 2A, 2B or 2C of odevixibat according to any one of claims 5 to 13 in a process for the preparation of crystal modification 1 of odevixibat according to claim 1.

15. A process for the preparation of crystal modification 1 of odevixibat according to claim 1, comprising isolating crystal modification 2A, 2B or 2C of odevixibat according to any one of claims 5 to 13 from a solution of odevixibat in a solvent mixture comprising water and an organic solvent selected from the group consisting of methanol, ethanol, 2-propanol, acetone, acetonitrile, 1,4-dioxane, DMF and DMSO.

16. The process according to claim 15, wherein the crystal modification 2 of odevixibat is crystal modification 2A of odevixibat.

17. The process according to claim 15 or 16, wherein crystal modification 2A of odevixibat is obtained from a mixture of water and ethanol.

18. The process according to claim 17, wherein the ethanol content in the solvent mixture is about 55 to about 75% (v/v).

19. A pharmaceutical composition comprising crystal modification 1 of odevixibat according to any one of claims 1 to 4, together with a pharmaceutically acceptable diluent or carrier.

20. Crystal modification 1 of odevixibat according to any one of claims 1 to 4, for use in therapy.

21. Use of crystal modification 1 of odevixibat according to any one of claims 1 to 4 in the manufacture of a medicament for the treatment or prevention of a cardiovascular disease or a disorder of fatty acid metabolism or a glucose utilization disorder, such as hypercholesterolemia; disorders of fatty acid metabolism; type 1 and type 2 diabetes mellitus; complications of diabetes, including cataracts, micro- and macrovascular diseases, retinopathy, neuropathy, nephropathy and delayed wound healing, tissue ischaemia, diabetic foot, arteriosclerosis, myocardial infarction, acute coronary syndrome, unstable angina pectoris, stable angina pectoris, stroke, peripheral arterial occlusive disease, cardiomyopathy, heart failure, heart rhythm disorders and vascular restenosis; diabetes-related diseases such as insulin resistance (impaired glucose homeostasis), hyperglycemia, hyperinsulinemia, elevated blood levels of fatty acids or glycerol, obesity, dyslipidemia, hyperlipidemia including hypertriglyceridemia, metabolic syndrome (syndrome X), atherosclerosis and hypertension; and for increasing high density lipoprotein levels.

22. Use of crystal modification 1 of odevixibat according to any one of claims 1 to 4 in the manufacture of a medicament for the treatment or prevention of a gastrointestinal disease or disorder, such as constipation (including chronic constipation, functional constipation, chronic idiopathic constipation (CIC), intermittent/sporadic constipation, constipation secondary to diabetes mellitus, constipation secondary to stroke, constipation secondary to chronic kidney disease, constipation secondary to multiple sclerosis, constipation secondary to Parkinson's disease, constipation secondary to systemic sclerosis, drug induced constipation, irritable bowel syndrome with constipation (IBS-C), irritable bowel syndrome mixed (IBS-M), pediatric functional constipation and opioid induced constipation); Crohn's disease; primary bile acid malabsorption; irritable bowel syndrome (IBS); inflammatory bowel disease (IBD); ileal inflammation; and reflux disease and complications thereof, such as Barrett's esophagus, bile reflux esophagitis and bile reflux gastritis.

23. Use of crystal modification 1 of odevixibat according to any one of claims 1 to 4 in the manufacture of a medicament for the treatment or prevention of a liver disease or disorder, such as an inherited metabolic disorder of the liver; inborn errors of bile acid synthesis; congenital bile duct anomalies; biliary atresia; post-Kasai biliary atresia; post-liver transplantation biliary atresia; neonatal hepatitis; neonatal cholestasis; hereditary forms of cholestasis; cerebrotendinous xanthomatosis; a secondary defect of BA synthesis; Zellweger´s syndrome; cystic fibrosis-associated liver disease; alpha1-antitrypsin deficiency; Alagilles

syndrome (ALGS); Byler syndrome; a primary defect of bile acid (BA) synthesis; progressive familial intrahepatic cholestasis (PFIC) including PFIC-1, PFIC-2, PFIC-3 and non-specified PFIC, post-biliary diversion PFIC and post-liver transplant PFIC; benign recurrent intrahepatic cholestasis (BRIC) including BRIC1, BRIC2 and non-specified BRIC, post-biliary diversion BRIC and post-liver transplant BRIC; autoimmune hepatitis; primary biliary cirrhosis (PBC); liver fibrosis; non-alcoholic fatty liver disease (NAFLD); non-alcoholic steatohepatitis (NASH); portal hypertension; cholestasis; Down syndrome cholestasis; drug-induced cholestasis; intrahepatic cholestasis of pregnancy (jaundice during pregnancy); intrahepatic cholestasis; extrahepatic cholestasis; parenteral nutrition associated cholestasis (PNAC); low phospholipid-associated cholestasis; lymphedema cholestasis syndrome 1 (LSC1); primary sclerosing cholangitis (PSC); immunoglobulin G4 associated cholangitis; primary biliary cholangitis; cholelithiasis (gall stones); biliary lithiasis; choledocholithiasis; gallstone pancreatitis; Caroli disease; malignancy of bile ducts; malignancy causing obstruction of the biliary tree; biliary strictures; AIDS cholangiopathy; ischemic cholangiopathy; pruritus due to cholestasis or jaundice; pancreatitis; chronic autoimmune liver disease leading to progressive cholestasis; hepatic steatosis; alcoholic hepatitis; acute fatty liver; fatty liver of pregnancy; drug-induced hepatitis; iron overload disorders; congenital bile acid synthesis defect type 1 (BAS type 1); drug-induced liver injury (DILI); hepatic fibrosis; congenital hepatic fibrosis; hepatic cirrhosis; Langerhans cell histiocytosis (LCH); neonatal ichthyosis sclerosing cholangitis (NISCH); erythropoietic protoporphyria (EPP); idiopathic adulthood ductopenia (IAD); idiopathic neonatal hepatitis (INH); non syndromic paucity of interlobular bile ducts (NS PILBD); North American Indian childhood cirrhosis (NAIC); hepatic sarcoidosis; amyloidosis; necrotizing enterocolitis; serum bile acid-caused toxicities, including cardiac rhythm disturbances (e.g., atrial fibrillation) in setting of abnormal serum bile acid profile, cardiomyopathy associated with liver cirrhosis ("cholecardia"), and skeletal muscle wasting associated with cholestatic liver disease; viral hepatitis (including hepatitis A, hepatitis B, hepatitis C, hepatitis D and hepatitis E); hepatocellular carcinoma (hepatoma); cholangiocarcinoma; bile acid-related gastrointestinal cancers; and cholestasis caused by tumours and neoplasms of the liver, of the biliary tract and of the pancreas.

24. Use of crystal modification 1 of odevixibat according to any one of claims 1 to 4 in the manufacture of a medicament for the treatment or prevention of hyperabsorption syndromes (including abetalipoproteinemia, familial hypobetalipoproteinemia (FHBL), chylomicron

retention disease (CRD) and sitosterolemia); hypervitaminosis and osteopetrosis; hypertension; glomerular hyperfiltration; and pruritus of renal failure.