EMA/156109/2015

Summary of the risk management plan (RMP) for Jinarc (tolvaptan)

This is a summary of the risk management plan (RMP) for Jinarc, which details the measures to be taken in order to ensure that Jinarc is used as safely as possible. For more information on RMP summaries, see here.

This RMP summary should be read in conjunction with the EPAR summary and the product information for Jinarc, which can be found on Jinarc's EPAR page.

Overview of disease epidemiology

Jinarc is a medicine used to treat adults with autosomal dominant polycystic kidney disease. This is an inherited disorder in which numerous fluid-filled cysts develop in the kidneys, which eventually affect kidney function and can cause the kidneys to fail. Symptoms of the disease usually develop between the ages of 20 to 50 years and include high blood pressure, pain due to infections of the urinary tract or stones forming in the kidneys. An estimated 45% to 70% of patients with the disease have kidney failure by the age of 65 years.

Over 12.5 million people worldwide are affected with polycystic kidney disease. The disease is caused by a defect in a gene and in most cases it is autosomal dominant, which means that a person can have the disease even if they have inherited the defective gene from only one parent. The condition affects males and females equally and it is seen in all ethnic groups.

Summary of treatment benefits

Jinarc contains the active substance tolvaptan. Tolvaptan works by blocking the action of a hormone, vasopressin, which regulates the level of water and sodium in the body and is thought to be responsible for the formation of fluid-filled cysts in autosomal dominant polycystic kidney disease.

Jinarc was shown to be effective at slowing down cyst formation in a main study involving 1,445 adults with autosomal dominant polycystic kidney disease who had rapidly progressing disease but normal or moderately reduced kidney function. In the study, Jinarc was compared with placebo (a dummy treatment) and the main measure of effectiveness was the change in kidney size after 3 years of treatment (a way of measuring the swelling caused by cyst formation). In patients taking placebo the total size of the kidneys increased by 18.8% whereas in those taking Jinarc the increase was 9.6%. The effects of treatment were greatest in the first year.

Unknowns relating to treatment benefits

The main study with Jinarc included adult patients with normal or moderately reduced kidney function. There is limited information on the efficacy of Jinarc in patients with severely reduced kidney function.

Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
Excessive loss of water from the body (Volume depletion and dehydration)	Loss of water in the body is due to the known effect of tolvaptan (the active substance in Jinarc) that helps the body get rid of water. Excessive loss of water which can lead to kidney failure was seen more frequently in patients receiving tolvaptan 15–60 mg (3.2%) than in the patients receiving placebo (2.4%). Thirst, dry mouth, low blood pressure and dizziness are some of the symptoms caused by excessive water loss.	Patients should be carefully watched for signs of excessive loss of water and they should be encouraged to drink plenty of water while taking Jinarc. In case of excessive loss of water, the doctor may interrupt or reduce the dose of Jinarc and ask the patient to increase their fluid intake. Jinarc should be used cautiously in patients who are at an increased risk of water loss (e.g. in case of vomiting or diarrhoea).
Kidney problems due to excessive loss of water from the body (Dehydration-associated renal dysfunction)	It is possible that serious events affecting the proper function of the kidneys could occur because of an excessive loss of body water in patients treated with tolvaptan who are not drinking enough. However, in clinical studies such serious events were seen in similar numbers in patients taking tolvaptan (5.0%) and placebo (5.7%).	Patients should be encouraged to drink plenty of water to avoid becoming dehydrated. If dehydration or kidney dysfunction occurs, the dose of Jinarc and/or other medicines that increase water loss in the urine (diuretics) may have to be reduced or interrupted.
Too rapid increase in the level of salt (sodium) in the blood leading to serious side effects affecting the brain (Rapid rise in serum sodium and neurological sequelae)	Jinarc can increase levels of sodium in the blood. If Jinarc is used in patients with low sodium levels (hyponatraemia) and sodium levels rise too quickly, swelling in the brain could occur which may lead to pressure in the brain and nerve demyelination (when the protective sheath around nerves is damaged) in certain parts of the brain. This could theoretically lead to serious side effects including fits, loss of consciousness and death.	This risk can be prevented by measuring blood sodium levels before and regularly during treatment and making appropriate dose adjustments to avoid rapid increases of blood sodium levels in patients with low sodium levels. Jinarc must not be used in patients who have hypernatraemia (increased sodium levels in the blood).
Increase in blood sugar and diabetes (Hyperglycaemia and diabetes mellitus)	In clinical studies, increases in blood sugar levels have been reported commonly (in more than 1 patient in 100) in patients taking Jinarc.	Since Jinarc may increase blood sugar levels, Jinarc should be used with caution in patients with diabetes, particularly those with inadequately controlled type 2 diabetes.

Risk	What is known	Preventability
Increased levels of uric acid in the blood (Hyperuricaemia)	Increased levels of uric acid in the blood are a common side effect (seen in more than 1 patient in 100) with Jinarc. Increased uric acid levels in the blood can lead to painful and swollen joints (gout).	Doctors should measure the levels of uric acid in the blood before starting treatment and should carefully monitor them during treatment.
Increased blood levels of potassium (hyperkalaemia) which can potentially lead to changes in heart rhythm in patients with heart disease (cardiac arrhythmias)	The water loss caused by tolvaptan can lead to increased levels of potassium in the blood which in turn could in theory lead to disturbances in the heart rhythm particularly in patients with certain heart conditions. Increased levels of potassium were a common side effect in clinical studies with Samsca (a medicine containing tolvaptan used for patients with low blood sodium levels).	Carefully monitoring blood levels of potassium and taking appropriate action when necessary.
Increased blood levels of salt (sodium) (Hypernatraemia)	The water loss caused by tolvaptan can lead to increased levels of salt (sodium) in the blood (hypernatraemia).	Jinarc must not be used in patients with increased sodium levels in the blood. Doctors should monitor the levels of sodium in the blood and ensure that patients have access to and are able to drink sufficient amounts of water. In patients unable to drink, fluid control under medical supervision is required.
Liver injury	In the main clinical study in patients with autosomal dominant polycystic kidney disease, more patients taking Jinarc were found to have increased levels of liver enzymes than patients taking placebo. Increased levels of these enzymes can indicate damage to the liver. Three cases were found to be serious liver injury. Levels of liver enzymes normalised within 1 to 4 months of stopping Jinarc treatment and were not associated with liver failure (when the liver stops working) or any permanent damage to the liver.	Blood tests to check the patient's liver function should be performed before starting treatment with Jinarc, and then repeated every month for 18 months and every three months thereafter. If significant increases in the liver enzymes are observed according to set criteria or if the patient has symptoms consistent with liver injury (e.g. fatigue, loss of appetite, nausea and vomiting, stomach pain/pain below the ribs, itchiness, dark urine, pale stools and yellow skin and eyes) treatment with Jinarc should be stopped.
Increased blood levels of tolvaptan when Jinarc is taken together with certain	Tolvaptan is broken down (metabolised) by specific enzymes in the liver called CYP3A4. Certain medicines (called CYP3A inhibitors) such as ketoconazole, macrolide	The dose of Jinarc should be reduced in patients while taking medicines that are moderate or strong CYP3A inhibitors.

Risk	What is known	Preventability
medicines (e.g. ketoconazole, macrolide antibiotics, diltiazem) or grapefruit juice that decrease the activity of specific enzymes (CYP3A4) in the liver responsible for breaking down (metabolising) tolvaptan	antibiotics, diltiazem block the activity of these enzymes and if they are taken together with Jinarc they can increase the amount of tolvaptan in the blood, thereby increasing its effects.	
Decreased blood levels of tolvaptan when Jinarc is taken together with certain medicines (e.g. barbiturates, rifampicin) that increase the activity of specific enzymes (CYP3A4) in the liver responsible for breaking down (metabolising) tolvaptan.	Tolvaptan is broken down (metabolised) by specific enzymes in the liver called CYP3A4. Certain medicines (called CYP3A inducers) such as barbiturates and rifampicin increase the activity of these enzymes and if they are taken together with Jinarc they can decrease the amount of tolvaptan in the blood. The amount of tolvaptan in the blood has been reduced by up to 85% after the use of a medicine called rifampicin. Taking Jinarc together with rifampicin or other medicines which increase its metabolism could lead to Jinarc not working properly.	Caution should be taken if Jinarc is taken with certain medicines called CYP3A inducers that increase the break down of tolvaptan.
Increased potassium levels in the blood when tolvaptan is used together with other medicines that also increase potassium (hyperkalaemia)	In clinical studies, the number of patients having high blood levels of potassium (hyperkalaemia) were slightly increased when tolvaptan was taken together with other medicines (aldosterone antagonists, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers) that increase potassium. However, this slight increase did not result in increased numbers of adverse outcomes such as heart arrhythmias or the heart stopping.	Carefully monitoring blood levels of potassium and the amount of fluids taken by the patient.
Jinarc can reduce the effect of	Jinarc blocks the action of the hormone vasopressin which acts on	It is not recommended to use Jinarc together with desmopressin or similar

Risk	What is known	Preventability
medicines, such as desmopressin, which are used to prevent or control bleeding	blood vessels to release substances involved in the blood clotting process. Certain medicines used to treat bleeding disorders (such as desmopressin) act in the same way as vasopressin in the blood vessels and their effects can be reduced if patients also take Jinarc.	medicines called vasopressin analogues.
Use of diuretics (medicines that increase water loss in the urine) together with Jinarc, leading to excessive loss of water from the body and reduced kidney function (dehydration and renal impairment)	Diuretic medicines as well as Jinarc increase the amount of water loss from the urine. If these medicines are used together it is possible that too much water may be lost (dehydration) which in some patients could lead to the kidneys not working properly. This is more likely to occur in patients who already have problems with their kidneys, in those patients who are not able to drink sufficient water or in those patients who already have increased loss of fluids.	Jinarc must not be given to patients who already have reduced amounts of fluids in the body (volume depletion). Patients should be encouraged to drink large volumes of water while taking Jinarc. If patients show signs of dehydration or kidney dysfunction, appropriate action must be taken which may include the interruption of treatment with Jinarc and/or diuretics.
Severe allergic reaction (anaphylaxis)	There was one case of a severe allergic reaction during the post-marking period with a potential causal association with Samsca (another medicine containing tolvaptan); no cases of severe allergic reactions were identified during clinical trials with Samsca or Jinarc.	If a serious allergic reaction occurs during treatment with Jinarc, treatment must be stopped immediately and appropriate therapy given. Patients with known or suspected hypersensitivity to tolvaptan or to any of the excipients must not take Jinarc.

Important potential risks

Risk	What is known
Retention of urine in patients with urinary outflow obstruction (e.g. in patients with an enlarged prostate gland or other urination disorders) (acute urinary retention)	Increased urination in the presence of urinary outflow obstruction, such as in patients with an enlarged prostate gland or other urination disorders, can potentially cause a backward flow of fluid initially in the bladder and if prolonged from the bladder to the upper urinary tract. However, in clinical studies the number of patients having an inability to urinate was similar between patients taking tolvaptan and placebo so at present this is a potential risk.
Increased risk of	Tolvaptan blocks the action of the hormone vasopressin, which could in

Risk	What is known
blood clotting and stroke in patients with heart disease (hypercoagulability, stroke)	turn lead to small increases in the amount of vasopressin within the body. As vasopressin also acts on cells in the blood which help clotting (platelets), this could lead to the formation of clots in blood vessels (thrombosis) and stroke. In clinical trials there was no overall increase in side effects due to the formation of clots, including heart attacks, in the tolvaptan-treated groups, so at present this is a potential risk.
Allergic skin reactions	Overall, the number of allergic skin reactions reported in clinical trials was low and similar between patients taking tolvaptan and placebo.
Raised pressure in the eye or an eye condition in which the nerve in the eye (optic nerve) is damaged affecting vision (raised intraocular pressure or glaucoma)	A clinical study showed that taking tolvaptan could lead to small increases in the amount of the hormone vasopressin in the blood. This hormone can activate specific proteins in the eye which in turn can cause the pressure in the eye to increase (raised intraocular pressure). Raised intraocular pressure can cause damage to a nerve in the eye (optic nerve) leading to an eye condition that can affect vision. In theory, tolvaptan could potentially cause these events but there has been no direct evidence of tolvaptan causing such events from the clinical studies.
Increased risk of stroke when Jinarc is given together with warfarin and antiplatelet agents	In the heart failure clinical studies with Samsca there was a slight increase in reports of stroke in patients who were taking tolvaptan together with both warfarin and antiplatelet agents (medicines that prevent blood clotting). No increase in the number of reports of stroke was found in patients who took tolvaptan with warfarin alone or tolvaptan with antiplatelet agents alone. Specific studies have not shown a significant interaction between warfarin and tolvaptan either. At present it is thought that the slight increase in the number of reports of stroke when tolvaptan, warfarin and antiplatelet medicines are taken together may be a chance finding rather than a real risk, but this potential risk will be monitored further.
Use of Jinarc together with medicines called angiotensin-converting enzyme inhibitors (e.g. ramipril, fosinopril, lisinopril, enalapril, benazepril) leading to dehydration	Jinarc and medicines called angiotensin-converting enzyme inhibitors (e.g. ramipril, fosinopril, lisinopril, enalapril, benazepril) cause the body to lose water. If these medicines are used together it is possible that excessive water may be lost (dehydration), which in some patients could lead to reduced levels of fluids in the body and the kidneys not working properly. This is more likely to occur in patients who already have problems with their kidneys or in those patients who are not able to drink sufficient water or in those patients who already have increased loss of fluids.
Use of Jinarc together with medicines called angiotensin receptor blockers (e.g. valsartan, candesartan, losartan) leading to dehydration	Jinarc and medicines called angiotensin receptor blockers (e.g. valsartan, candesartan, losartan) cause the body to lose water. If these medicines are used together it is possible that excessive water may be lost (dehydration) which in some patients could lead to reduced levels of fluids in the body and the kidneys not working properly. This is more likely to occur in patients who already have problems with their kidneys or in those patients who are not able to drink sufficient water or in those patients who

Risk	What is known
	already have increased loss of fluids.
Disturbances in heart rhythm due to changes in electrolytes (sodium, potassium, magnesium, calcium) in heart failure patients (cardiac arrhythmias)	The water loss caused by tolvaptan can lead to increased levels of potassium which in turn could in theory lead to disturbances in the heart rhythm particularly in patients with an existing heart condition. Increased levels of potassium were a common side effect in the Samsca clinical studies and it was seen at greater frequencies in patients receiving Samsca than in patients receiving inactive medication. However, there were no reports of heart rhythm changes.
Reduced blood supply to the heart after stopping Jinarc treatment in worsening heart failure patients (myocardial ischaemia)	Use of tolvaptan can lead to small increases in the amount of the hormone vasopressin circulating within the body which acts on platelets (cells that help the blood to clot) leading to blood clotting. A theoretical concern is that, when treatment with tolvaptan is stopped, the initial reduction in the levels of vasopressin may trigger the blood to clot more and lead to a potential risk of the blood flow to the heart muscle being reduced in patients with worsening heart failure. In the clinical studies, side effects relating to reduced blood flow to the heart muscle after discontinuing Samsca were reported in less than 0.3% of patients. Most of the patients who experienced these events were patients with existing heart failure.
Breathlessness in heart failure patients (dyspnoea)	In clinical studies, there were a slightly higher number of cases of breathlessness in patients with heart failure being treated with tolvaptan than with placebo. Breathlessness is one of the major symptoms of heart failure so the significance of the slight increase noted in the heart failure patients treated with tolvaptan is not clear but it is considered an important potential risk in these patients.
Bleeding in the stomach or gut in patients with liver scarring (liver cirrhosis)	A higher number of patients with scarring (cirrhosis) of the liver treated with tolvaptan had side effects related to gastrointestinal (stomach and gut) bleeding than those receiving placebo. However, combined data from all of the patients studied in clinical trials showed fewer side effects related to gastrointestinal bleeding in tolvaptan-treated patients than in those receiving placebo.
Skin tumours/skin cancer (skin neoplasm/basal cell carcinoma)	In clinical trials a higher number of patients with autosomal dominant polycystic kidney disease who received treatment with Jinarc reported having skin cancer (mainly a type called basal cell carcinoma) than those treated with placebo. However, a causal relationship has not been established.
Risk of malformation in the unborn child	When very high doses of tolvaptan (15 times the recommended human daily dose) were given to rabbits there were increased numbers of certain malformations in the offspring. Women of childbearing potential should use adequate contraceptive measures when being treated with Jinarc. Jinarc must not be used in pregnancy.

Missing information

Risk	What is known
Limited information in children	Children under the age of 18 years have not been treated with Jinarc and use in children is not recommended.
Limited information in pregnant women	The experience in pregnant women is too small to draw any conclusions. Jinarc must not be used in pregnancy. Women of childbearing potential must use effective methods of contraception during treatment with Jinarc.
No information in breastfeeding women and infants who were breastfed while their mother was taking Jinarc	The potential risk for babies who are being breastfed is unknown. In animal studies, tolvaptan was transferred to breast milk. Jinarc must not be taken by breastfeeding mothers.
Use outside the approved use (off-label use)	Jinarc should only be used to treat adults with autosomal dominant polycystic kidney disease. Information on how well Jinarc works in other conditions or what side effects could be seen are not available.
Use in patients with liver impairment	There is limited information in patients with liver impairment.
Use in patients with autosomal dominant polycystic kidney disease that is not stage 1 to 3	Limited clinical data on the benefit of Jinarc in patients with more severe (stage 4) disease are available, and no clinical data are available in patients with severe kidney insufficiency or in patients who are unable to make urine. Jinarc treatment should be discontinued if kidney diseases progresses to stage 5.
Use of Jinarc in patients over 50 years	Data are not available on the safety and effectiveness of Jinarc in patients over 50 years of age.
Long-term use of Jinarc in clinical practice	Long-term data on the safety and effectiveness of Jinarc are not currently available.

Summary of risk minimisation measures by safety concern

All medicines have a summary of product characteristics (SmPC) which provides physicians, pharmacists and other healthcare professionals with details on how to use the medicine, and also describes the risks and recommendations for minimising them. Information for patients is available in lay language in the package leaflet. The measures listed in these documents are known as 'routine risk minimisation measures'.

The SmPC and the package leaflet are part of the medicine's product information. The product information for Jinarc can be found on Jinarc's EPAR page.

This medicine has special conditions and restrictions for its safe and effective use (additional risk minimisation measures). Full details on these conditions and the key elements of any educational

material can be found in Annex II of the product information which is published on Jinarc's EPAR page; how they are implemented in each country however will depend upon agreement between the marketing authorisation holder and the national authorities.

These additional risk minimisation measures are for the following risks:

Safety concern: Damage to the liver (Liver injury)

Risk minimisation measure: Educational programme
Objective and rationale: To ensure that doctors and patients are aware of the risk of liver injury with Jinarc, to provide guidance on how to manage this risk and to highlight the importance of pregnancy prevention before and during treatment with Jinarc.
Description: • All healthcare professionals and patients expected to use Jinarc should be provided with educational material containing information on the risk of liver injury and the importance of pregnancy prevention. • Patients should also be given an alert card with information on: – the early signs and symptoms of liver injury – what to do if such symptoms occur

Planned post-authorisation development plan

List of studies in post-authorisation development plan

Study / activity (including study number)	**Objectives**	**Safety concerns / efficacy issue addressed**	**Status**	**Planned date for submission of (interim and) final results**
In vitro study to investigate the potential of tolvaptan metabolites, DM-4103 and DM-4107, to inhibit the transporter known as P-gp	The aim of the study is to determine how likely the metabolites are to inhibit the function of the P-gp transporter	Other medicines are transported by P-gp and tolvaptan administration may alter the elimination profile of these medicines	Ongoing	Final report: Aug 2016
Study 156-14-216: A study in healthy subjects to determine if moderate inhibition of the drug metabolizing enzyme CYP3A	The aim of the study is to determine the effect of the moderate CYP3A inhibitor fluconazole at 400 mg and 200 mg doses on tolvaptan concentrations in	Tolvaptan concentrations are increased about 4-fold with strong CYP3A inhibitors; the effect of moderate inhibitors is unknown and therefore proper dose reductions of tolvaptan when co-	Planned	Final report: Aug 2016

Study / activity (including study number)	Objectives	Safety concerns / efficacy issue addressed	Status	Planned date for submission of (interim and) final results
increases tolvaptan concentrations	healthy subjects	administered with these compounds is not known		
Study 156-12-299: Jinarc post-authorization safety study (PASS)	The aim of this PASS study is to assess long-term safety of Jinarc when used in a real-life setting in the treatment of patients with autosomal dominant polycystic kidney disease	Liver injury and other identified and potential risks, including glaucoma and skin neoplasms. In addition, morbidity and mortality related to autosomal dominant polycystic kidney disease	Planned	Final report: Q4 2022
Study 156-08-271: A multicenter, open-label, extension study (Extension of trial 156-04-251)	The aim of this study is to evaluate the long-term safety and efficacy of oral Jinarc tablet regimens in patients with autosomal dominant polycystic kidney disease	Long-term safety and efficacy of Jinarc	Ongoing	Final report: 30 June 2016
Protocol 156-13-210: A Phase 3b, multicenter, randomized-withdrawal, placebo-controlled, double-blind parallel-group trial	The aim of this study is to compare the efficacy and safety of Jinarc in subjects with chronic kidney disease between late stage 2 to early stage 4 due to autosomal dominant polycystic kidney disease	Efficacy and safety of Jinarc in subjects with chronic kidney disease due to autosomal dominant polycystic kidney disease	Ongoing	Final report: 15 Feb 2018

Studies which are a condition of the marketing authorisation

Studies 156-12-299, 156-08-271 and 156-13-210 are conditions of the marketing authorisation of Jinarc.

Summary of changes to the risk management plan over time

Not applicable.

This summary was last updated in 04-2015.