SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Posaconazole 300 mg concentrate for solution for infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 300 mg of posaconazole. Each ml contains 18 mg of posaconazole.

Excipient with known effect:
Each vial contains up to 477 mg (20.75 mmol) sodium.
Each vial contains 6680 mg of cyclodextrin (as Betadex Sulfobutyl Ether Sodium (SBECD)).

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Concentrate for solution for infusion.
Clear, colourless or slightly yellow liquid.
pH: 2.2 - 3.0
Osmolarity: 2250-2750 mOsmol/kg

4.1 Therapeutic indications

Posaconazole 300 mg concentrate for solution for infusion is indicated for use in the treatment of the following fungal infections in adults (see sections 4.2 and 5.1):

- Invasive aspergillosis

Posaconazole 300 mg concentrate for solution for infusion is indicated for use in the treatment of the following fungal infections in adult and paediatric patients from 2 years of age (see sections 4.2 and 5.1):

- Invasive aspergillosis in patients with disease that is refractory to amphotericin B or itraconazole or in patients who are intolerant of these medicinal products;
- Fusariosis in patients with disease that is refractory to amphotericin B or in patients who are intolerant of amphotericin B;
- Chromoblastomycosis and mycetoma in patients with disease that is refractory to itraconazole or in patients who are intolerant of itraconazole;
- Coccidioidomycosis in patients with disease that is refractory to amphotericin B, itraconazole or fluconazole or in patients who are intolerant of these medicinal products.

Refractoriness is defined as progression of infection or failure to improve after a minimum of 7 days of prior therapeutic doses of effective antifungal therapy.

Posaconazole 300 mg concentrate for solution for infusion is also indicated for prophylaxis of invasive fungal infections in the following adult and paediatric patients from 2 years of age (see sections 4.2 and 5.1):

- Patients receiving remission-induction chemotherapy for acute myelogenous leukemia (AML) or myelodysplastic syndromes (MDS) expected to result in prolonged neutropenia and who are at high risk of developing invasive fungal infections;
- Hematopoietic stem cell transplant (HSCT) recipients who are undergoing high-dose immunosuppressive therapy for graft versus host disease (GVHD) and who are at high risk of developing invasive fungal infections.

Please refer to the Summary of Product Characteristics of posaconazole oral suspension products for use in oropharyngeal candidiasis.

4.2 Posology and method of administration

Treatment should be initiated by a physician experienced in the management of fungal infections or in the supportive care in the high risk patients for which posaconazole is indicated as prophylaxis.

Posology

Posaconazole is also available for oral administration (oral suspension, gastro-resistant tablet). A switch to oral administration is recommended as soon as the patients' condition allows (see section 4.4).
Recommended dose is shown in Table 1.

Table 1. Recommended dose according to indication

Indication	**Dose and duration of therapy**
Treatment of invasive aspergillosis (only for adults)	Loading dose of 300 mg Posaconazole (300 mg concentrate for solution for infusion or three 100 mg tablets) twice a day on the first day, then 300 mg (300 mg concentrate for solution for infusion or three 100 mg tablets) once a day thereafter. Each tablet dose may be taken without regard to food intake. Recommended total duration of therapy is 6-12 weeks. Switching between intravenous and oral administration is appropriate when clinically indicated.
Refractory invasive fungal infections (IFI)/patients with IFI intolerant to 1st line therapy	**Adults:** Loading dose of 300 mg Posaconazole twice a day on the first day, then 300 mg once a day thereafter. Duration of therapy should be based on the severity of the underlying disease, recovery from immunosuppression, and clinical response. **Paediatric patients aged 2 to less than 18 years:** Loading dose of 6 mg/kg (to a maximum of 300 mg) twice a day on the first day, then 6 mg/kg (to a maximum of 300 mg) once a day thereafter. Duration of therapy should be based on the severity of the underlying disease, recovery from immunosuppression, and clinical response.

Prophylaxis of invasive fungal infections	**Adults:** Loading dose of 300 mg Posaconazole twice a day on the first day, then 300 mg once a day thereafter. Duration of therapy is based on recovery from neutropenia or immunosuppression. For patients with AML or MDS, prophylaxis with Posaconazole 300 mg should start several days before the anticipated onset of neutropenia and continue for 7 days after the neutrophil count rises above 500 cells per mm^3. **Paediatric patients aged 2 to less than 18 years:** Loading dose of 6 mg/kg (to a maximum of 300 mg) twice a day on the first day, then 6 mg/kg (to a maximum of 300 mg) once a day thereafter. Duration of therapy is based on recovery from neutropenia or immunosuppression. For patients with acute myelogenous leukaemia or myelodysplastic syndromes, prophylaxis with Posaconazole 300 mg should start several days before the anticipated onset of neutropenia and continue

Posaconazole 300 mg should be administered via a central venous line, including a central venous catheter or peripherally inserted central catheter (PICC) by slow intravenous infusion over approximately 90 minutes. Posaconazole 300 mg concentrate for solution for infusion should not be given by bolus administration. If a central venous catheter is not available, a single infusion may be administered through a peripheral venous catheter. When administered through a peripheral venous catheter, the infusion should be administered over approximately 30 minutes (see section 4.8 and 6.6).

Special populations

Renal impairment
In patients with moderate or severe renal impairment (creatinine clearance <50 mL/min), accumulation of the intravenous vehicle, Betadex Sulfobutyl Ether Sodium (SBECD), is expected to occur. Oral formulations of Posaconazole should be used in these patients unless an assessment of the benefit/risk to the patient justifies the use of Posaconazole 300 mg concentrate for solution for infusion. Serum creatinine levels should be closely monitored in these patients (see section 4.4).

Hepatic impairment
Limited data on the effect of hepatic impairment (including Child-Pugh C classification of chronic liver disease) on the pharmacokinetics of posaconazole demonstrate an increase in plasma exposure compared to subjects with normal hepatic function, but do not suggest that dose adjustment is necessary (see sections 4.4 and 5.2). It is recommended to exercise caution due to the potential for higher plasma exposure.

Paediatric population
The safety and efficacy of Posaconazole 300 mg concentrate for solution for infusion in children aged below 2 years have not been established. No clinical data are available.
Posaconazole 300 mg concentrate for solution for infusion should not be used in children aged below 2 years because of pre-clinical safety concerns (see section 5.3).

Method of administration

Posaconazole 300 mg concentrate for solution for infusion requires dilution (see section 6.6) prior to administration. Posaconazole 300 mg should be administered via a central venous line, including a central venous catheter or peripherally inserted central catheter (PICC) by slow intravenous (IV) infusion over approximately 90 minutes (see sections 4.2, 4.4, and 4.8).
Posaconazole 300 mg concentrate for solution for infusion should not be given by bolus administration.
If a central venous catheter is not available, a single infusion may be administered through a peripheral venous catheter. When administered through a peripheral venous catheter, the infusion should be administered over approximately 30 minutes to reduce the likelihood of infusion site reactions (see section 4.8).

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Co-administration with ergot alkaloids (see section 4.5).

Co-administration with the CYP3A4 substrates terfenadine, astemizole, cisapride, pimozide, halofantrine or quinidine since this may result in increased plasma concentrations of these medicinal products, leading to QTc prolongation and rare occurrences of torsades de pointes (see sections 4.4 and 4.5).

Co-administration with the HMG-CoA reductase inhibitors simvastatin, lovastatin and atorvastatin (see section 4.5).

Co-administration during the initiation and dose-titration phase of venetoclax in Chronic Lymphocytic Leukaemia (CLL) patients (see sections 4.4 and 4.5).

4.4 Special warnings and precautions for use

Hypersensitivity

There is no information regarding cross-sensitivity between posaconazole and other azole antifungal agents. Caution should be used when prescribing Posaconazole 300 mg to patients with hypersensitivity to other azoles.

Hepatictoxicity

Hepatic reactions (e.g. elevations in ALT, AST, alkaline phosphatase, total bilirubin and/or clinical hepatitis) have been reported during treatment with posaconazole. Elevated liver function tests were generally reversible on discontinuation of therapy and in some instances these tests normalised without interruption of therapy. Rarely, more severe hepatic reactions with fatal outcomes have been reported.

Posaconazole should be used with caution in patients with hepatic impairment due to limited clinical experience and the possibility that posaconazole plasma levels may be higher in these patients (see sections 4.2 and 5.2).

Monitoring of patients with severe renal impairment

Due to the variability in exposure, patients with severe renal impairment should be monitored closely for breakthrough fungal infections (see sections 4.2 and 5.2).

Monitoring of hepatic function

Liver function tests should be evaluated at the start of and during the course of posaconazole therapy. Patients who develop abnormal liver function tests during Posaconazole 300 mg therapy must be routinely monitored for the development of more severe hepatic injury. Patient management should include laboratory evaluation of hepatic function (particularly liver function tests and bilirubin).

Discontinuation of Posaconazole 300 mg should be considered if clinical signs and symptoms are consistent with development of liver disease.

QTc prolongation

Some azoles have been associated with prolongation of the QTc interval. Posaconazole 300 mg must not be administered with medicinal products that are substrates for CYP3A4 and are known to prolong the QTc interval (see sections 4.3 and 4.5). Posaconazole 300 mg should be administered with caution to patients with pro-arrhythmic conditions such as:

- Congenital or acquired QTc prolongation
- Cardiomyopathy, especially in the presence of cardiac failure
- Sinus bradycardia
- Existing symptomatic arrhythmias
- Concomitant use with medicinal products known to prolong the QTc interval (other than those mentioned in section 4.3).

Electrolyte disturbances, especially those involving potassium, magnesium or calcium levels, should be monitored and corrected as necessary before and during posaconazole therapy.

In patients, mean maximum plasma concentrations (C_{max}) after posaconazole concentrate for solution for infusion are 4-fold increased compared to administration of oral suspension. An increased effect on the QTc interval cannot be ruled out. Particular caution is advised in such cases where posaconazole is administered peripherally, as the recommended infusion time of 30 minutes may further increase C_{max}.

Drug Interactions

Posaconazole is an inhibitor of CYP3A4 and should only be used under specific circumstances during treatment with other medicinal products that are metabolised by CYP3A4 (see section 4.5).

Midazolam and other benzodiazepines

Due to the risk of prolonged sedation and possible respiratory depression co-administration of posaconazole with any benzodiazepines metabolised by CYP3A4 (e.g. midazolam, triazolam, alprazolam) should only be considered if clearly necessary. Dose adjustment of benzodiazepines metabolised by CYP3A4 should be considered (see section 4.5).

Vincristine toxicity

Concomitant administration of azole antifungals, including posaconazole, with vincristine has been associated with neurotoxicity and other serious adverse reactions, including seizures, peripheral neuropathy, syndrome of inappropriate antidiuretic hormone secretion, and paralytic ileus. Reserve azole antifungals, including posaconazole, for patients receiving a vinca alkaloid, including vincristine, who have no alternative antifungal treatment options (see section 4.5).

Venetoclax toxicity
Concomitant administration of strong CYP3A inhibitors, including posaconazole, with the CYP3A4 substrate venetoclax, may increase venetoclax toxicities, including the risk of tumour lysis syndrome (TLS) and neutropenia (see sections 4.3 and 4.5). Refer to the venetoclax SmPC for detailed guidance.

Rifamycin antibacterials (rifampicin,rifabutin), flucloxacillin, certain anticonvulsants (phenytoin,carbamazepine, phenobarbital,primidone) and efavirenz
Posaconazole concentrations may be significantly lowered in combination; therefore, concomitant use with posaconazole should be avoided unless the benefit to the patient outweighs the risk (see section 4.5).

Photosensitivity reaction
Posaconazole may cause increased risk of photosensitivity reaction. Patients should be advised to avoid sun exposure during treatment without adequate protection, such as protective clothing and sunscreen with a high sun protection factor (SPF).

Plasma exposure
Plasma concentrations following administration of posaconazole intravenous concentrate for solution for infusion are generally higher than those obtained with posaconazole oral suspension.
Posaconazole plasma concentrations following administration of posaconazole may increase over time in some patients (see section 5.2).

Thromboembolic events
Thromboembolic events have been identified as a potential risk for posaconazole intravenous concentrate for solution for infusion but were not observed in the clinical studies. Thrombophlebitis was observed in clinical trials. Caution is warranted on any sign or symptom of thromboembolic events (see sections 4.8 and 5.3).

Sodium content
This medicinal product contains 477 mg sodium per vial, equivalent to 23.8% of the WHO recommended maximum daily intake of 2 g sodium for an adult.
Posaconazole 300 mg is considered high in sodium. This should be particularly taken into account for those on a low salt diet.

Cyclodextrin(s) content
This medicinal product contains 6680 mg cyclodextrin(s) in each vial which is equivalent to 6680 mg/16.7 ml.

4.5 Interaction with other medicinal products and other forms of interaction

The following information was derived from data with posaconazole oral suspension or early tablet formulation. All drug interactions with posaconazole oral suspension, except for those that affect the absorption of posaconazole (via gastric pH and motility) are considered relevant to posaconazole concentrate for solution for infusion as well.

Effects of other medicinal products on posaconazole
Posaconazole is metabolised via UDP glucuronidation (phase 2 enzymes) and is a substrate for p-glycoprotein (P-gp) efflux *in vitro*. Therefore, inhibitors (e.g. verapamil, ciclosporin, quinidine, clarithromycin, erythromycin, etc.) or inducers (e.g.

rifampicin, rifabutin, certain anticonvulsants, etc.) of these clearance pathways may increase or decrease posaconazole plasma concentrations, respectively.

Rifabutin
Rifabutin (300 mg once a day) decreased the C_{max} (maximum plasma concentration) and AUC (area under the plasma concentration time curve) of posaconazole to 57 % and 51 %, respectively. Concomitant use of posaconazole and rifabutin and similar inducers (e.g. rifampicin) should be avoided unless the benefit to the patient outweighs the risk. See also below regarding the effect of posaconazole on rifabutin plasma levels.

Efavirenz
Efavirenz (400 mg once a day) decreased the C_{max} and AUC of posaconazole by 45 % and 50 %, respectively. Concomitant use of posaconazole and efavirenz should be avoided unless the benefit to the patient outweighs the risk.

Fosamprenavir
Combining fosamprenavir with posaconazole may lead to decreased posaconazole plasma concentrations. If concomitant administration is required, close monitoring for breakthrough fungal infections is recommended. Repeat dose administration of fosamprenavir (700 mg twice daily x 10 days) decreased the C_{max} and AUC of posaconazole oral suspension (200 mg once daily on the 1st day, 200 mg twice daily on the 2nd day, then 400 mg twice daily x 8 Days) by 21 % and 23 %, respectively. The effect of posaconazole on fosamprenavir levels when fosamprenavir is given with ritonavir is unknown.

Phenytoin
Phenytoin (200 mg once a day) decreased the C_{max} and AUC of posaconazole by 41 % and 50 %, respectively. Concomitant use of posaconazole and phenytoin and similar inducers (e.g. carbamazepine, phenobarbital, primidone) should be avoided unless the benefit to the patient outweighs the risk.

Flucloxacillin
Flucloxacillin (a CYP450 inducer) may decrease plasma posaconazole concentrations. Concomitant use of posaconazole with flucloxacillin should be avoided unless the benefit to the patient outweighs the risk (see section 4.4).

<u>Effects of posaconazole on other medicinal products</u>
Posaconazole is a potent inhibitor of CYP3A4. Co-administration of posaconazole with CYP3A4 substrates may result in large increases in exposure to CYP3A4 substrates as exemplified by the effects on tacrolimus, sirolimus, atazanavir and midazolam below. Caution is advised during co- administration of posaconazole with CYP3A4 substrates administered intravenously and the dose of the CYP3A4 substrate may need to be reduced. If posaconazole is used concomitantly with CYP3A4 substrates that are administered orally, and for which an increase in plasma concentrations may be associated with unacceptable adverse reactions, plasma concentrations of the CYP3A4 substrate and/or adverse reactions should be closely monitored and the dose adjusted as needed.

Terfenadine, astemizole, cisapride, pimozide, halofantrine and quinidine (CYP3A4 substrates)

Co-administration of posaconazole and terfenadine, astemizole, cisapride, pimozide, halofantrine or quinidine is contraindicated. Co-administration may result in increased plasma concentrations of these medicinal products, leading to QTc prolongation and rare occurrences of torsades de pointes (see section 4.3).

Ergot alkaloids
Posaconazole may increase the plasma concentration of ergot alkaloids (ergotamine and dihydroergotamine), which may lead to ergotism. Co-administration of posaconazole and ergot alkaloids is contraindicated (see section 4.3).

HMG-CoA reductase inhibitors metabolised through CYP3A4 (e.g. simvastatin, lovastatin, and atorvastatin)
Posaconazole may substantially increase plasma levels of HMG-CoA reductase inhibitors that are metabolised by CYP3A4. Treatment with these HMG-CoA reductase inhibitors should be discontinued during treatment with posaconazole as increased levels have been associated with rhabdomyolysis (see section 4.3).

Vinca alkaloids
Most of the vinca alkaloids (e.g., vincristine and vinblastine) are substrates of CYP3A4. Concomitant administration of azole antifungals, including posaconazole, with vincristine has been associated with serious adverse reactions (see section 4.4). Posaconazole may increase the plasma concentrations of vinca alkaloids which may lead to neurotoxicity and other serious adverse reactions. Therefore, reserve azole antifungals, including posaconazole, for patients receiving a vinca alkaloid, including vincristine, who have no alternative antifungal treatment options.

Rifabutin
After oral administration, posaconazole increased the C_{max} and AUC of rifabutin by 31 % and 72 %, respectively. Concomitant use of posaconazole and rifabutin should be avoided unless the benefit to the patient outweighs the risk (see also above regarding the effect of rifabutin on plasma levels of posaconazole). If these medicinal products are co-administered, careful monitoring of full blood counts and adverse reactions related to increased rifabutin levels (e.g. uveitis) is recommended.

Sirolimus
Repeat dose administration of oral posaconazole oral suspension (400 mg twice daily for 16 days) increased the C_{max} and AUC of sirolimus (2 mg single dose) an average of 6.7-fold and 8.9-fold (range 3.1 to 17.5-fold), respectively, in healthy subjects. The effect of posaconazole on sirolimus in patients is unknown, but is expected to be variable due to the variable posaconazole exposure in patients. Co- administration of posaconazole with sirolimus is not recommended and should be avoided whenever possible. If it is considered that co-administration is unavoidable, then it is recommended that the dose of sirolimus should be greatly reduced at the time of initiation of posaconazole therapy and that there should be very frequent monitoring of trough concentrations of sirolimus in whole blood. Sirolimus concentrations should be measured upon initiation, during co-administration, and at discontinuation of posaconazole treatment, with sirolimus doses adjusted accordingly**.** It should be noted that the relationship between sirolimus trough concentration and AUC is changed during co- administration with posaconazole. As a result, sirolimus trough concentrations that fall within the usual therapeutic range may result in sub-therapeutic levels. Therefore trough concentrations that fall in the upper part of the usual therapeutic range should be targeted and careful attention should be paid to clinical signs and symptoms, laboratory parameters and tissue biopsies.

Ciclosporin
In heart transplant patients on stable doses of ciclosporin, posaconazole oral suspension 200 mg once daily increased ciclosporin concentrations requiring dose reductions. Cases of elevated ciclosporin levels resulting in serious adverse reactions, including nephrotoxicity and one fatal case of leukoencephalopathy, were reported in clinical efficacy studies. When initiating treatment with posaconazole in patients already receiving ciclosporin, the dose of ciclosporin should be reduced (e.g. to about three quarters of the current dose). Thereafter blood levels of ciclosporin should be monitored carefully during co-administration, and upon discontinuation of posaconazole treatment, and the dose of ciclosporin should be adjusted as necessary.

Tacrolimus
Posaconazole increased C_{max} and AUC of tacrolimus (0.05 mg/kg body weight single dose) by 121 % and 358 %, respectively. Clinically significant interactions resulting in hospitalisation and/or posaconazole discontinuation were reported in clinical efficacy studies. When initiating posaconazole treatment in patients already receiving tacrolimus, the dose of tacrolimus should be reduced (e.g. to about one third of the current dose). Thereafter blood levels of tacrolimus should be monitored carefully during co-administration, and upon discontinuation of posaconazole, and the dose of tacrolimus should be adjusted as necessary.

HIV Protease inhibitors
As HIV protease inhibitors are CYP3A4 substrates, it is expected that posaconazole will increase plasma levels of these antiretroviral agents. Following co-administration of posaconazole oral suspension (400 mg twice daily) with atazanavir (300 mg once daily) for 7 days in healthy subjects C_{max} and AUC of atazanavir increased by an average of 2.6-fold and 3.7-fold (range 1.2 to 26-fold), respectively. Following co-administration of posaconazole oral suspension (400 mg twice daily) with atazanavir and ritonavir (300/100 mg once daily) for 7 days in healthy subjects C_{max} and AUC of atazanavir increased by an average of 1.5-fold and 2.5-fold (range 0.9 to 4.1-fold), respectively. The addition of posaconazole to therapy with atazanavir or with atazanavir plus ritonavir was associated with increases in plasma bilirubin levels. Frequent monitoring for adverse reactions and toxicity related to antiretroviral agents that are substrates of CYP3A4 is recommended during co- administration with posaconazole.

Midazolam and other benzodiazepines metabolised by CYP3A4
In a study in healthy volunteers posaconazole oral suspension (200 mg once daily for 10 days) increased the exposure (AUC) of intravenous midazolam (0.05 mg/kg) by 83 %. In another study in healthy volunteers, repeat dose administration of posaconazole oral suspension (200 mg twice daily for 7 days) increased the C_{max} and AUC of intravenous midazolam (0.4 mg single dose) by an average of 1.3- and 4.6-fold (range 1.7 to 6.4-fold), respectively; Posaconazole oral suspension 400 mg twice daily for 7 days increased the intravenous midazolam C_{max} and AUC by 1.6 and 6.2-fold (range 1.6 to 7.6-fold), respectively. Both doses of posaconazole increased C_{max} and AUC of oral midazolam (2 mg single oral dose) by 2.2 and 4.5-fold, respectively. In addition, posaconazole oral suspension (200 mg or 400 mg) prolonged the mean terminal half-life of midazolam from approximately 3-4 hours to 8-
10 hours during co-administration.
Due to the risk of prolonged sedation it is recommended that dose adjustments should be considered when posaconazole is administered concomitantly with any

benzodiazepine that is metabolised by CYP3A4 (e.g. midazolam, triazolam, alprazolam) (see section 4.4).

Calcium channel blockers metabolised through CYP3A4 (e.g. diltiazem, verapamil, nifedipine, nisoldipine)
Frequent monitoring for adverse reactions and toxicity related to calcium channel blockers is recommended during co-administration with posaconazole. Dose adjustment of calcium channel blockers may be required.

Digoxin
Administration of other azoles has been associated with increases in digoxin levels. Therefore, posaconazole may increase plasma concentration of digoxin and digoxin levels need to be monitored when initiating or discontinuing posaconazole treatment.

Sulfonylureas
Glucose concentrations decreased in some healthy volunteers when glipizide was co-administered with posaconazole. Monitoring of glucose concentrations is recommended in diabetic patients.

All-trans retinoic acid (ATRA) or tretinoin
As ATRA is metabolised by the hepatic CYP450 enzymes, notably CYP3A4, concomitant administration with posaconazole, which is a strong inhibitor of CYP3A4, may lead to increased exposure to tretinoin resulting in an increased toxicity (especially hypercalcaemia). Serum calcium levels should be monitored and, if needed, appropriate dose adjustments of tretinoin should be considered during the treatment with posaconazole, and during the following days after treatment.

Venetoclax
Compared with venetoclax 400 mg administered alone, co-administration of 300 mg posaconazole, a strong CYP3A inhibitor, with venetoclax 50 mg and 100 mg for 7 days in 12 patients, increased venetoclax Cmax to 1.6-fold and 1.9-fold, and AUC to 1.9-fold and 2.4-fold, respectively (see sections 4.3 and 4.4). Refer to the venetoclax SmPC.

Paediatric population
Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and lactation

Pregnancy
There is insufficient information on the use of posaconazole in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown.

Women of childbearing potential have to use effective contraception during treatment. Posaconazole must not be used during pregnancy unless the benefit to the mother clearly outweighs the potential risk to the foetus.

Breast-feeding
Posaconazole is excreted into the milk of lactating rats (see section 5.3). The excretion of posaconazole in human breast milk has not been investigated. Breast-feeding must be stopped on initiation of treatment with posaconazole.

Fertility

Posaconazole had no effect on fertility of male rats at doses up to 180 mg/kg (2.8 times the exposure achieved from a 300 mg intravenous dose in human) or female rats at a dose up to 45 mg/kg (3.4 times the exposure from a 300 mg intravenous dose in patients). There is no clinical experience assessing the impact of posaconazole on fertility in humans.

4.7 Effects on ability to drive and use machines

Since certain adverse reactions (e.g. dizziness, somnolence, etc.) have been reported with posaconazole use, which potentially may affect driving/operating machinery, caution needs to be used.

4.8 Undesirable effects

Summary of the safety profile

Safety data mainly derive from studies with the oral suspension.
The safety of posaconazole oral suspension has been assessed in > 2,400 patients and healthy volunteers enrolled in clinical studies and from post-marketing experience. The most frequently reported serious related adverse reactions included nausea, vomiting, diarrhoea, pyrexia, and increased bilirubin.

Posaconazole concentrate for solution for infusion

The safety of posaconazole concentrate for solution for infusion has been assessed in 72 healthy volunteers and 268 patients enrolled in a clinical study of antifungal prophylaxis.
The safety of posaconazole concentrate for solution for infusion and posaconazole tablet has been assessed in 288 patients enrolled in a clinical study of aspergillosis of whom 161 patients received the concentrate for solution for infusion and 127 patients received the tablet formulation.

Posaconazole 300 mg concentrate for solution for infusion was investigated in AML and MDS patients and those after HSCT with or at risk for GVHD only. Maximum duration of exposure to the concentrate for solution for infusion was shorter than with the oral suspension. Plasma exposure resulting from the solution for infusion was higher than observed with the oral suspension. A higher incidence of adverse reactions cannot be ruled out.

In initial studies of healthy volunteers, administration of a single dose of posaconazole infused over 30 minutes via a peripheral venous catheter was associated with a 12 % incidence of infusion site reactions (4 % incidence of thrombophlebitis). Multiple doses of posaconazole administered via a peripheral venous catheter were associated with thrombophlebitis (60 % incidence). Therefore, in subsequent studies posaconazole was administered via central venous catheter. If a central venous catheter was not readily available, patients could receive a single infusion over 30 minutes via a

peripheral venous catheter. Peripheral infusion time longer than 30 minutes, leads to a higher incidence of infusion site reactions and thrombophlebitis.
The safety of posaconazole concentrate for solution for infusion has been assessed in 268 patients in clinical trials. Patients were enrolled in a non-comparative pharmacokinetic and safety trial of posaconazole concentrate for solution for infusion when given as antifungal prophylaxis (Study 5520). Eleven patients received a single dose of 200 mg posaconazole concentrate for solution for infusion, 21 patients received 200 mg daily dose for a median of 14 days, and 237 patients received 300 mg daily dose for a median of 9 days. No safety data are available for administration > 28 days. Safety data in the elderly are limited.

The most frequently reported adverse reaction (>25 %) with an onset during the posaconazole intravenous phase of dosing with 300 mg once daily was diarrhoea (32 %).

The most common adverse reaction (>1 %) leading to discontinuation of posaconazole concentrate for solution for infusion 300 mg once daily was AML (1 %).

The safety of posaconazole tablets and concentrate for solution for infusion were also investigated in a controlled study of treatment of invasive aspergillosis. The maximum duration of invasive aspergillosis treatment was similar to that studied with the oral suspension for salvage treatment and was longer than that with the tablets or concentrate for solution for infusion in prophylaxis.

Posaconazole gastro-resistant powder and solvent for oral suspension and concentrate for solution for infusion safety
The safety of posaconazole gastro-resistant powder and solvent for oral suspension and concentrate for solution for infusion has been assessed in 115 paediatric patients aged 2 to less than 18 years for prophylaxis use. Immunocompromised paediatric patients with known or expected neutropenia were exposed to posaconazole at 3.5 mg/kg, 4.5 mg/kg or 6 mg/kg.
Reported adverse reactions were generally consistent with those expected in a paediatric oncology population undergoing treatment for malignancy or with the safety profile of posaconazole in adults.
The most frequently reported adverse reactions (>2%) during treatment were alanine aminotransferase increased (2.6%), aspartate aminotransferase increased (3.5%) and rash (2.6%).

Tabulated list of adverse reactions
Within the organ system classes, adverse reactions are listed under headings of frequency using the following categories: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥ 1/10,000 to <1/1,000); very rare (<1/10,000); not known (cannot be estimated from the available data).

Table 2. Adverse reactions by body system and frequency reported in clinical trials and/or post- marketing use*

Blood and lymphatic system disorders Common: Uncommon: Rare:	neutropenia thrombocytopenia, leukopenia, anaemia, eosinophilia, lymphadenopathy, splenic infarction haemolytic uraemic syndrome, thrombotic thrombocytopenic purpura, pancytopenia, coagulopathy,
Immune system disorders Uncommon: Rare:	allergic reaction hypersensitivity
Endocrine disorders Rare:	adrenal insufficiency, blood gonadotropin decreased, pseudoaldosteronism
Metabolism and nutrition disorders Common:	electrolyte imbalance, anorexia, decreased appetite, hypokalaemia, hypomagnesaemia hyperglycaemia, hypoglycaemia
Psychiatric disorders Uncommon: Rare:	abnormal dreams, confusional state, sleep disorder psychotic disorder, depression
Nervous system disorders Common: Uncommon: Rare:	paresthesia, dizziness, somnolence, headache, dysgeusia convulsions, neuropathy, hypoaesthesia, tremor, aphasia, insomnia cerebrovascular accident, encephalopathy, peripheral
Eye disorders Uncommon:	blurred vision, photophobia, visual acuity reduced diplopia, scotoma
Ear and labyrinth disorder Rare:	hearing impairment
Cardiac disorders Uncommon: Rare:	long QT syndrome[§], electrocardiogram abnormal[§], palpitations, bradycardia, supraventricular extrasystoles, tachycardia torsade de pointes, sudden death, ventricular tachycardia, cardio-respiratory arrest, cardiac failure, myocardial
Vascular disorders Common: Uncommon:	hypertension hypotension, thrombophlebitis, vasculitis pulmonary embolism, deep vein thrombosis
Respiratory, thoracic and mediastinal disorders Uncommon: Rare:	cough, epistaxis, hiccups, nasal congestion, pleuritic pain, tachypnoea pulmonary hypertension, interstitial pneumonia,

Gastrointestinal disorders Very Common Common: Uncommon : 	 nausea vomiting, abdominal pain, diarrhoea, dyspepsia, dry mouth, flatulence, constipation, anorectal discomfort pancreatitis, abdominal distension, enteritis, epigastric discomfort, eructation, gastrooesophageal reflux disease, oedema mouth gastrointestinal haemorrhage, ileus
Hepatobiliary disorders Common: Uncommon: Rare: 	 liver function tests raised (ALT increased, AST increased, bilirubin increased, alkaline phosphatase increased, GGT increased) hepatocellular damage, hepatitis, jaundice, hepatomegaly, cholestasis, hepatic toxicity, hepatic function abnormal hepatic failure, hepatitis cholestatic, hepatosplenomegaly, liver tenderness, asterixis
Skin and subcutaneous tissue disorders Common: Uncommon : Rare: Not known:	 rash, pruritis mouth ulceration, alopecia, dermatitis, erythema, petechiae Stevens Johnson syndrome, vesicular rash [§]
Musculoskeletal and connective tissue disorders Uncommon:	 back pain, neck pain, musculoskeletal pain, pain in extremity
Renal and urinary disorders Uncommon: Rare:	 acute renal failure, renal failure, blood creatinine increased renal tubular acidosis, interstitial nephritis
Reproductive system and breast disorders Uncommon: Rare:	 menstrual disorder breast pain
General disorders and administration site conditions Common: Uncommon: Rare:	 pyrexia (fever), asthenia, fatigue oedema, pain, chills, malaise, chest discomfort, drug intolerance, feeling jittery, infusion site pain, infusion site phlebitis, infusion site thrombosis, mucosal inflammation tongue oedema, face oedema
Investigations Uncommon:	 altered medicine levels, blood phosphorus decreased, chest x- ray abnormal

* Based on adverse reactions observed with the oral suspension, gastro-resistant tablets, and concentrate for solution for infusion.

[§] See section 4.4.

Description of selected adverse reactions

Hepatobiliary disorders

During post-marketing surveillance severe hepatic injury with fatal outcome has been reported (see section 4.4).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card scheme at www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

There is no experience with overdose of posaconazole concentrate for solution for infusion.

During clinical trials, patients who received posaconazole oral suspension doses up to 1,600 mg/day experienced no different adverse reactions from those reported with patients at the lower doses. Accidental overdose was noted in one patient who took posaconazole oral suspension 1,200 mg twice a day for 3 days. No adverse reactions were noted by the investigator.

Posaconazole is not removed by haemodialysis. There is no special treatment available in the case of overdose with posaconazole. Supportive care may be considered.

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antimycotics for systemic use, triazole derivatives, ATC code: J02A C04.

Mechanism of action

Posaconazole inhibits the enzyme lanosterol 14α-demethylase (CYP51), which catalyses an essential step in ergosterol biosynthesis.

Microbiology

Posaconazole has been shown *in vitro* to be active against the following microorganisms: *Aspergillus* species (*Aspergillus fumigatus, A. flavus, A. terreus, A. nidulans, A. niger, A. ustus*), *Candida* species (*C. albicans, C. glabrata, C. krusei, C. parapsilosis, C. tropicalis, C. dubliniensis, C. famata, C. inconspicua, C. lipolytica, C. norvegensis, C. pseudotropicalis*), *Coccidioides immitis*, *Fonsecaea pedrosoi*, and species of *Fusarium*, *Rhizomucor*, *Mucor*, and *Rhizopus.* The microbiological data suggest that posaconazole is active against *Rhizomucor*, *Mucor*, and *Rhizopus;* however the clinical data are currently too limited to assess the efficacy of posaconazole against these causative agents.
The following *in vitro* data are available, but their clinical significance is unknown. In a surveillance study of > 3,000 clinical mold isolates from 2010-2018, 90% of non-*Aspergillus* fungi exhibited the following *in vitro* minimum inhibitory concentration (MIC): *Mucorales* spp (n=81) of 2 mg/L; *Scedosporium apiospermum/S. boydii* (n=65) of 2 mg/L; *Exophiala dermatiditis* (n=15) of 0.5 mg/L, and *Purpureocillium lilacinum* (n=21) of 1 mg/L.

Resistance

Clinical isolates with decreased susceptibility to posaconazole have been identified. The principle mechanism of resistance is the acquisition of substitutions in the target protein, CYP51.

Epidemiological Cut-off (ECOFF) values for *Aspergillus spp*.
The ECOFF values for posaconazole, which distinguish the wild type population from isolates with acquired resistance, have been determined by EUCAST methodology.

EUCAST ECOFF values:
- *Aspergillus flavus*: 0.5 mg/L
- *Aspergillus fumigatus*: S ≤0.125 mg/L, R >0.25 mg/L, ATU=0.25 mg/L
- *Aspergillus nidulans*: 0.5 mg/L
- *Aspergillus niger*: 0.5 mg/L
- *Aspergillus terreus*: S ≤0.125 mg/L, R >0.25 mg/L, ATU=0.25 mg/L

There are currently insufficient data to set clinical breakpoints for *Aspergillus* spp. ECOFF values do not equate to clinical breakpoints.

Susceptibility testing breakpoints
MIC (minimum inhibitory concentration) interpretive criteria for susceptibility testing have been established by the European Committee on Antimicrobial Susceptibility Testing (EUCAST) for posaconazole and are listed here:
https://www.ema.europa.eu/documents/other/minimum-inhibitory-concentration-mic-breakpoints_en.xlsx

Combination with other antifungal agents
The use of combination antifungal therapies should not decrease the efficacy of either posaconazole or the other therapies; however, there is currently no clinical evidence that combination therapy will provide an added benefit.

Clinical experience

Summary of posaconazole concentrate for solution for infusion bridging study
Study 5520 was a non-comparative multi-center study performed to evaluate the pharmacokinetic properties, safety, and tolerability of posaconazole concentrate for solution for infusion.

Study 5520 enrolled a total of 279 subjects, including 268 receiving at least one dose of posaconazole concentrate for solution for infusion. Cohort 0 was designed to evaluate the tolerability of a single dose of posaconazole concentrate for solution for infusion when administered via a central line.
The subject population for Cohorts 1 and 2 included subjects with AML or MDS who had recently received chemotherapy and had developed or were anticipated to develop significant neutropenia. Two different dosing groups were evaluated in Cohorts 1 and 2: 200 mg twice daily on Day 1, followed by 200 mg once daily thereafter (Cohort 1) and 300 mg twice daily on Day 1, followed by 300 mg once daily thereafter (Cohort 2).

The subject population in Cohort 3 included: 1) patients with AML or MDS who had recently received chemotherapy and had developed or were anticipated to develop significant neutropenia, or 2) patients who had undergone a HSCT and were receiving immunosuppressive therapy for prevention or treatment of GVHD. These

types of patients had been previously studied in a pivotal controlled trial of posaconazole oral suspension. Based on the pharmacokinetics and safety results of Cohorts 1 and 2, all subjects in Cohort 3 received 300 mg twice daily on Day 1, followed by 300 mg once daily thereafter.

The total subject population had a mean age of 51 years (range = 18-82 years), 95 % were White, the major ethnicity was not Hispanic or Latino (92 %), and 55 % were male. The study treated 155 (65 %) subjects with AML or MDS, and 82 (35 %) subjects with HSCT, as the primary diseases at study entry.

Serial pharmacokinetic samples were collected on Day 1 and at steady-state on Day 14 for all Cohort 1 and 2 subjects and on Day 10 for a subset of Cohort 3 subjects. This serial pharmacokinetic analysis demonstrated that 94 % of the subjects treated with the 300 mg once daily dose attained steady state Cav between 500-2500 ng/mL [Cav was the average concentration of posaconazole at steady state, calculated as AUC/dosing interval (24 hours).]. This exposure was selected based on pharmacokinetic/pharmacodynamic considerations with posaconazole oral suspension. Subjects who received 300 mg once daily achieved a mean Cav at steady state of 1500 ng/mL.

Summary of posaconazole concentrate for solution for infusion and tablet study invasive aspergillosis

The safety and efficacy of posaconazole for the treatment of patients with invasive aspergillosis was evaluated in a double-blind controlled study (study-69) in 575 patients with proven, probable, or possible invasive fungal infections per EORTC/MSG criteria.

Patients were treated with posaconazole (n=288) concentrate for solution for infusion or tablet given at a dose of 300 mg QD (BID on Day 1). Comparator patients were treated with voriconazole (n=287) given IV at a dose of 6 mg/kg BID Day 1 followed by 4 mg/kg BID of voriconazole (intravenous), or orally at a dose of 300 mg BID Day 1 followed by 200 mg BID. Median treatment duration was 67 days (posaconazole) and 64 days (voriconazole).

In the intent-to-treat (ITT) population (all subjects who received at least one dose of study drug), 288 patients received posaconazole and 287 patients received voriconazole. The full analysis set population (FAS) is the subset of all subjects within the ITT population who were classified by independent adjudication as having proven or probable invasive aspergillosis: 163 subjects for posaconazole and 171 subjects for voriconazole. The all-cause mortality and global clinical response in these two populations are presented in Table 3 and 4, respectively.

Table 3. Posaconazole invasive aspergillosis treatment study 1: all-cause mortality at Day 42 and Day 84, in the ITT and FAS populations

	Posaconazole		**Voriconazole**		
Population	N	n (%)	N	n (%)	Difference* (95 % CI)
Mortality in ITT at Day 42	288	44 (15.3)	287	59 (20.6)	-5.3 % (-11.6, 1.0)
Mortality in ITT at Day 84	288	81 (28.1)	287	88 (30.7)	-2.5 % (-9.9, 4.9)
Mortality in FAS at Day	163	31 (19.0)	171	32 (18.7)	0.3% (-8.2, 8.8)

42					
Mortality in FAS at Day 84	163	56 (34.4)	171	53 (31.0)	3.1% (-6.9, 13.1)
* Adjusted treatment difference based on Miettinen and Nurminen's method stratified by randomisation factor (risk for mortality/poor outcome), using Cochran-Mantel-Haenszel weighting scheme.					

Table 4. Posaconazole invasive aspergillosis treatment study 1: global clinical response at Week 6 and Week 12 in the FAS population

	Posaconazole		**Voriconazole**		
Population	N	Success (%)	N	Success (%)	Difference* (95 % CI)
Global clinical response in the FAS at 6 weeks	163	73 (44.8)	171	78 (45.6)	-0.6 % (-11.2, 10.1)
Global clinical response in the FAS at 12 weeks	163	69 (42.3)	171	79 (46.2)	-3.4 % (-13.9, 7.1)
* Successful Global Clinical Response was defined as survival with a partial or complete response Adjusted treatment difference based on Miettinen and Nurminen's method stratified by randomisation factor (risk for mortality/poor outcome), using Cochran-Mantel-Haenszel weighting scheme.					

Summary of gastro-resistant powder and solvent for oral suspension and concentrate for solution for infusion bridging study

The pharmacokinetics and safety of posaconazole concentrate for solution for infusion and gastroresistant powder and solvent for oral suspension have been assessed in 115 paediatric subjects aged 2 to less than 18 years in a non-randomised, multi-centre, open-label, sequential dose-escalation study (Study 097). Immunocompromised paediatric subjects with known or expected neutropenia were exposed to posaconazole at 3.5 mg/kg, 4.5 mg/kg or 6.0 mg/kg daily (BID on Day 1). All 115 subjects initially received posaconazole concentrate for solution for infusion for at least 7 days, and 63 subjects were transitioned to gastro-resistant powder and solvent for oral suspension. The mean overall treatment duration (posaconazole concentrate for solution for infusion and gastro-resistant powder and solvent for oral suspension) of all treated subjects was 20.6 days (see section 5.2).

Summary of posaconazole oral suspension studies

Invasive aspergillosis

Oral posaconazole suspension 800 mg/day in divided doses was evaluated for the treatment of invasive aspergillosis in patients with disease refractory to amphotericin B (including liposomal formulations) or itraconazole or in patients who were intolerant of these medicinal products in a non- comparative salvage therapy trial. Clinical outcomes were compared with those in an external control group derived from a retrospective review of medical records. The external control group included 86 patients treated with available therapy (as above) mostly at the same time and at the same sites as the patients treated with posaconazole. Most of the cases of aspergillosis were considered to be refractory to prior therapy in both the posaconazole group (88 %) and in the external control group (79 %).

As shown in Table 5, a successful response (complete or partial resolution) at the end of treatment was seen in 42 % of posaconazole-treated patients compared to 26 % of the external group. However, this was not a prospective, randomised controlled study and so all comparisons with the external control group should be viewed with caution.

Table 5. Overall efficacy of posaconazole oral suspension at the end of treatment for invasive aspergillosis in comparison to an external control group

	Posaconazole oral suspension		External control group	
Overall Response	45/107 (42 %)		22/86 (26 %)	
Success by Species				
All mycologically confirmed *Aspergillus* spp.[3]	34/76	(45 %)	19/74	(26 %)
A. fumigatus	12/29	(41 %)	12/34	(35 %)
A. flavus	10/19	(53 %)	3/16	(19 %)
A. terreus	4/14	(29 %)	2/13	(15 %)
A. niger	3/5	(60 %)	2/7	(29 %)

[3] Includes other less common species or species unknown

Fusarium spp.
11 of 24 patients who had proven or probable fusariosis were successfully treated with posaconazole oral suspension 800 mg/day in divided doses for a median of 124 days and up to 212 days. Among eighteen patients who were intolerant or had infections refractory to amphotericin B or itraconazole, seven patients were classed as responders.

Chromoblastomycosis/Mycetoma
9 of 11 patients were successfully treated with posaconazole oral suspension 800 mg/day in divided doses for a median of 268 days and up to 377 days. Five of these patients had chromoblastomycosis due to *Fonsecaea pedrosoi* and 4 had mycetoma, mostly due to *Madurella* species.

Coccidioidomycosis
11 of 16 patients were successfully treated (at the end of treatment complete or partial resolution of signs and symptoms present at baseline*)* with posaconazole oral suspension 800 mg/day in divided doses for a median of 296 days and up to 460 days.

Prophylaxis of Invasive Fungal Infections (IFIs) (Studies 316 and 1899)
Two randomised, controlled prophylaxis studies were conducted among patients at high risk for developing invasive fungal infections.

Study 316 was a randomised, double-blind trial of posaconazole oral suspension (200 mg three times a day) versus fluconazole capsules (400 mg once daily) in allogeneic hematopoietic stem cell transplant recipients with graft-versus-host disease (GVHD). The primary efficacy endpoint was the incidence of proven/probable IFIs at 16 weeks post-randomisation as determined by an independent, blinded external expert panel. A key secondary endpoint was the incidence of proven/probable IFIs during the on-treatment period (first dose to last dose of study medicinal product + 7 days). The majority (377/600, [63 %]) of patients included had Acute Grade 2 or 3 or chronic extensive (195/600, [32.5 %]) GVHD at study start. The mean duration of therapy was 80 days for posaconazole and 77 days for fluconazole.

Study 1899 was a randomised, evaluator-blinded study of posaconazole oral suspension (200 mg three times a day) versus fluconazole suspension (400 mg once daily) or itraconazole oral solution (200 mg twice a day) in neutropenic patients who were receiving cytotoxic

chemotherapy for acute myelogenous leukaemia or myelodysplastic syndromes. The primary efficacy endpoint was the incidence of proven/probable IFIs as determined by an independent, blinded external expert panel during the on-treatment period. A key secondary endpoint was the incidence of proven/probable IFIs at 100 days post-randomisation. New diagnosis of acute myelogenous leukaemia was the most common underlying condition (435/602, [72 %]). The mean duration of therapy was 29 days for posaconazole and 25 days for fluconazole/itraconazole.

In both prophylaxis studies, aspergillosis was the most common breakthrough infection. See Table 4 and 5 for results from both studies. There were fewer breakthrough *Aspergillus* infections in patients receiving posaconazole prophylaxis when compared to control patients.

Table 6. Results from clinical studies in prophylaxis of Invasive Fungal Infections

Study	Posaconazole oral suspension	Control[a]	P-Value
Proportion (%) of patients with proven/probable IFIs			
On-treatment period[b]			
1899[d]	7/304 (2)	25/298 (8)	0.0009
316[e]	7/291 (2)	22/288 (8)	0.0038
Fixed-time period[c]			
1899[d]	14/304 (5)	33/298 (11)	0.0031
316 [d]	16/301 (5)	27/299 (9)	0.0740

FLU = fluconazole; ITZ = itraconazole; POS = posaconazole.

a: FLU/ITZ (1899); FLU (316).

b: In 1899 this was the period from randomisation to last dose of study medicinal product plus 7 days; in 316 it was the period from first dose to last dose of study medicinal product plus 7 days.

c: In 1899, this was the period from randomisation to 100 days post-randomisation; in 316 it was the period from the baseline day to 111 days post-baseline.

d: All randomised e: All treated

Table 7. Results from clinical studies in prophylaxis of Invasive Fungal Infections

Study	Posaconazole oral suspension	Control[a]
Proportion (%) of patients with proven/probable Aspergillosis		
On-treatment period[b]		
1899[d]	2/304 (1)	20/298 (7)
316[e]	3/291 (1)	17/288 (6)
Fixed-time period[c]		
1899[d]	4/304 (1)	26/298 (9)
316 [d]	7/301 (2)	21/299 (7)

FLU = fluconazole; ITZ = itraconazole; POS = posaconazole.

a: FLU/ITZ (1899); FLU (316).

b: In 1899 this was the period from randomisation to last dose of study medicinal product plus 7 days; in 316 it was the period from first dose to last dose of study medicinal product plus 7 days.

c: In 1899, this was the period from randomisation to 100 days post-randomisation; in 316 it was the period from the baseline day to 111 days post-baseline.

d: All randomised

e: All treated

In Study 1899, a significant decrease in all cause mortality in favour of posaconazole was observed [POS 49/304 (16 %) vs. FLU/ITZ 67/298 (22 %) p= 0.048]. Based on Kaplan-Meier estimates, the probability of survival up to day 100 after randomisation, was significantly

higher for posaconazole recipients; this survival benefit was demonstrated when the analysis considered all causes of death (P= 0.0354) as well as IFI-related deaths (P = 0.0209).

In Study 316, overall mortality was similar (POS, 25 %; FLU, 28 %); however, the proportion of IFI- related deaths was significantly lower in the POS group (4/301) compared with the FLU group (12/299; P= 0.0413).

Paediatric population
There is limited paediatric experience for posaconazole concentrate for solution for infusion.

Three patients 14-17 years of age were treated with posaconazole concentrate for solution for infusion and tablet 300 mg/day (BID on Day 1 followed by QD thereafter) in the study of treatment of invasive aspergillosis.
The safety and efficacy of posaconazole (gastro-resistant powder and solvent for oral suspension; concentrate for solution for infusion) have been established in paediatric patients 2 to less than 18 years of age. Use of posaconazole in these age groups is supported by evidence from adequate and well-controlled studies of posaconazole in adults and pharmacokinetic and safety data from paediatric studies (see section 5.2). No new safety signals associated with the use of posaconazole in paediatric patients were identified in the paediatric studies (see section 4.8).

Safety and efficacy in paediatric patients below the age of 2 years have not been established. No data are available.

Electrocardiogram evaluation
Multiple, time-matched ECGs collected over a 12 hour period were obtained before and during administration of posaconazole oral suspension (400 mg twice daily with high fat meals) from 173 healthy male and female volunteers aged 18 to 85 years. No clinically relevant changes in the mean QTc (Fridericia) interval from baseline were observed.

5.2 Pharmacokinetic properties

Pharmacokinetic/Pharmacodynamic relationships
A correlation between total medicinal product exposure divided by MIC (AUC/MIC) and clinical outcome was observed. The critical ratio for subjects with *Aspergillus* infections was ~200. It is particularly important to try to ensure that maximal plasma levels are achieved in patients infected with *Aspergillus* (see sections 4.2 and 5.2 on recommended dose regimens).

Distribution
Following administration of 300 mg posaconazole concentrate for solution for infusion over 90 minutes, mean peak plasma concentration at the end of infusion was 3280 ng/mL (74 % CV). Posaconazole exhibits dose proportional pharmacokinetics after single and multiple dosing in the therapeutic dose range (200-300 mg). Posaconazole has a distribution volume of 261 L, indicating extravascular distribution.

Posaconazole is highly protein bound (> 98 %), predominantly to serum albumin.

Biotransformation

Posaconazole does not have any major circulating metabolites. Of the circulating metabolites, the majority are glucuronide conjugates of posaconazole with only minor amounts of oxidative (CYP450 mediated) metabolites observed. The excreted metabolites in urine and faeces account for approximately 17 % of the administered radiolabelled dose of posaconazole oral suspension.

Elimination

Posaconazole, after administration of 300 mg of posaconazole concentrate for solution for infusion, is slowly eliminated with a mean half-life ($t_{½}$) of 27 hours and a mean clearance of 7.3 L/hr. After administration of ^{14}C-posaconazole as oral suspension, radioactivity was predominantly recovered in the faeces (77 % of the radiolabelled dose) with the major component being parent compound (66 % of the radiolabelled dose). Renal clearance is a minor elimination pathway, with 14 % of the radiolabelled dose excreted in urine (< 0.2 % of the radiolabelled dose is parent compound). Steady- state plasma concentrations are attained by Day 6 at the 300 mg dose (once daily after twice daily loading dose at Day 1).

Posaconazole plasma concentrations following administration of posaconazole concentrate for solution for infusion single dose increased in a greater than dose proportional manner over the range of 50-200 mg; by comparison, dose-dependent increases were observed over a range of 200-300 mg.

Pharmacokinetics in special populations

Based on a population pharmacokinetic model evaluating posaconazole pharmacokinetics, steady state posaconazole concentrations were predicted in patients administered posaconazole concentrate for solution for infusion or tablets 300 mg once a day following BID dosing on Day 1 for the treatment of invasive aspergillosis and prophylaxis of invasive fungal infections.

Table 8. Population predicted median (10th percentile, 90th percentile) posaconazole steady state plasma concentrations in patients following administration of posaconazole concentrate for solution for infusion or tablets 300 mg QD (BID on Day 1)

Regimen	**Population**	**C_{av} (ng/mL)**	**C_{min} (ng/mL)**
Tablet-(Fasted)	Prophylaxis	1,550 (874; 2,690)	1,330 (667; 2,400)
	Treatment of Invasive Aspergillosis	1,780 (879; 3,540)	1,490 (663; 3,230)
Concentrate for Solution for Infusion	Prophylaxis	1,890 (1,100; 3,150)	1,500 (745; 2,660)
	Treatment of Invasive Aspergillosis	2,240 (1,230; 4,160)	1,780 (874; 3,620)

The population pharmacokinetic analysis of posaconazole in patients suggests that race, sex, renal impairment and disease (prophylaxis or treatment) have no clinically meaningful effect on the pharmacokinetics of posaconazole.

Children (< 18 years)

There is limited (n=3) paediatric experience with posaconazole concentrate for solution for infusion in the study of treatment of invasive aspergillosis (see sections 4.2 and 5.3).
The mean pharmacokinetic parameters after multiple dose administration of posaconazole concentrate for solution for infusion and posaconazole gastro-resistant powder and solvent for oral suspension in neutropenic paediatric patients 2 to less than 18 years of age are shown in Table 9. Patients were enrolled into 2 age groups and received posaconazole concentrate for solution for infusion and posaconazole gastro-resistant powder and solvent for oral suspension doses at 6 mg/kg (maximum 300 mg) once daily (twice daily on Day 1) (see section 5.1).

Table 9. Summary of Steady-State Geometric Mean Pharmacokinetic Parameters (% Geometric CV) After Multiple Dosing with Posaconazole Concentrate for Solution for Infusion and Posaconazole Gastro-Resistant Powder and Solvent for Oral Suspension 6 mg/kg in Paediatric Patients with Neutropenia or Expected Neutropenia

Age Group	**Dose Type**	**N**	**$AUC_{0\text{-}24\ hours}$ (ng· hr/mL)**	**C_{av}* (ng/mL)**	**C_{max} (ng/mL)**	**C_{min} (ng/mL)**	**T_{max}† (hr)**	**CL/F‡ (L/hr)**
2 to <7 years	IV	17	31,100 (48.9)	1,300 (48.9)	3,060 (54.1)	626 (104.8)	1.75 (1.57-1.83)	3.27 (49.3)
	PFS	7	23,000 (47.3)	960 (47.3)	1,510 (43.4)	542 (68.8)	4.00 (2.17-7.92)	4.60 (35.2)
7 to 17 years	IV	24	44,200 (41.5)	1,840 (41.5)	3,340 (39.4)	1,160 (60.4)	1.77 (1.33-6.00)	4.76 (55.7)
	PFS	12	25,000 (184.3)	1,040 (184.3)	1,370 (178.5)	713 (300.6)	2.78 (0.00-4.00)	8.39 (190.3)

IV= posaconazole concentrate for solution for infusion; PFS=posaconazole gastro-resistant powder and solvent for oral suspension; $AUC_{0\text{-}24\ hours}$ = Area under the plasma concentration-time curve from time zero to 24 hr; C_{max} = maximum observed concentration; C_{min} = minimum observed plasma concentration; T_{max} = time of maximum observed concentration; CL /F = apparent total body clearance
* C_{av} = time-averaged concentrations (i.e., $AUC_{0\text{-}24\ hours}$/24hr)
† Median (minimum-maximum)
‡ Clearance (CL for IV and CL/F for PFS)

Based on a population pharmacokinetic model evaluating posaconazole pharmacokinetics and predicting exposures in paediatric patients, the exposure target of steady-state posaconazole average concentration (Cav) of approximately 1,200 ng/mL and Cav ≥ 500 ng/mL in approximately 90% of patients is attained with the recommended dose of posaconazole concentrate for solution for infusion and gastro-resistant powder and solvent for oral suspension. Simulations, using the population pharmacokinetic model, predict a Cav ≥ 500 ng/mL in 90% of paediatric patients weighing at least 40 kg following administration of the adult dose of posaconazole gastro-resistant tablets (300 mg twice daily on Day 1 and 300 mg once daily starting on Day 2).
The population pharmacokinetic analysis of posaconazole in paediatric patients suggests that age, sex, renal impairment and ethnicity have no clinically meaningful effect on the pharmacokinetics of posaconazole.

Gender
The pharmacokinetics of posaconazole concentration for solution for infusion are comparable in men and women.

Elderly
The pharmacokinetics of posaconazole concentrate for solution for infusion are comparable in young and elderly subjects (≥ 65 years of age). No overall differences in safety were observed between the geriatric patients and younger patients.
The population pharmacokinetic model of posaconazole concentrate for solution for infusion and tablets indicates that posaconazole clearance is related to age. Posaconazole Cav is generally comparable between young and elderly patients (≥ 65 years of age); however, the Cav is increased by 11% in the very elderly (≥ 80 years). It is, therefore, suggested to closely monitor very elderly patients (≥ 80 years) for adverse events.
Pharmacokinetic differences based upon age are not to be considered clinically relevant; therefore, no dosage adjustment is required for geriatric patients.

Race
There is insufficient data among different races with posaconazole concentrate for solution for infusion.

There was a slight decrease (16 %) in the AUC and C_{max} of posaconazole oral suspension in Black subjects relative to Caucasian subjects. However, the safety profile of posaconazole between the Black and Caucasian subjects was similar.

Weight
The population pharmacokinetic model of posaconazole concentrate for solution for infusion and tablets indicates that posaconazole clearance is related to weight. In patients > 120 kg, the Cav is decreased by 25% and in patients < 50 kg, the Cav is increased by 19%. It is, therefore, suggested to closely monitor for breakthrough fungal infections in patients weighing more than 120 kg.

Renal impairment
Following single-dose administration of posaconazole oral suspension, there was no effect of mild and moderate renal impairment (n=18, $Cl_{cr} \geq 20$ mL/min/1.73 m^2) on posaconazole pharmacokinetics; therefore, no dose adjustment is required. In subjects with severe renal impairment (n=6, $Cl_{cr} < 20$ mL/min/1.73 m^2), the AUC of posaconazole was highly variable [> 96 % CV (coefficient of variance)] compared to other renal groups [< 40 % CV]. However, as posaconazole is not significantly renally eliminated, an effect of severe renal impairment on the pharmacokinetics of posaconazole is not expected and no dose adjustment is recommended. Posaconazole is not removed by haemodialysis. Due to the variability in exposure, patients with severe renal impairment should be monitored closely for breakthrough fungal infections (see section 4.2).

Similar recommendations apply to posaconazole concentrate for solution for infusion; however, a specific study has not been conducted with posaconazole concentrate for solution for infusion.

Hepatic impairment
After a single oral dose of 400 mg posaconazole oral suspension to patients with mild (Child-Pugh Class A), moderate (Child-Pugh Class B) or severe (Child-Pugh Class C) hepatic impairment (six per group), the mean AUC was 1.3 to 1.6-fold higher

compared to that for matched control subjects with normal hepatic function. Unbound concentrations were not determined and it cannot be excluded that there is a larger increase in unbound posaconazole exposure than the observed 60 % increase in total AUC. The elimination half-life ($t^{1/2}$) was prolonged from approximately 27 hours up to ~43 hours in respective groups. No dose adjustment is recommended for patients with mild to severe hepatic impairment but caution is advised due to the potential for higher plasma exposure.

Similar recommendations apply to posaconazole concentrate for solution for infusion; however, a specific study has not been conducted with posaconazole concentrate for solution for infusion.

5.3 Preclinical safety data

As observed with other azole antifungal agents, effects related to inhibition of steroid hormone synthesis were seen in repeated-dose toxicity studies with posaconazole. Adrenal suppressive effects were observed in toxicity studies in rats and dogs at exposures equal to or greater than those obtained at therapeutic doses in humans.

Neuronal phospholipidosis occurred in dogs dosed for □ 3 months at lower systemic exposures than those obtained at therapeutic doses in humans. This finding was not seen in monkeys dosed for one year. In twelve-month neurotoxicity studies in dogs and monkeys, no functional effects were observed on the central or peripheral nervous systems at systemic exposures greater than those achieved therapeutically.

Pulmonary phospholipidosis resulting in dilatation and obstruction of the alveoli was observed in the 2-year study in rats. These findings are not necessarily indicative of a potential for functional changes in humans.

No effects on electrocardiograms, including QT and QTc intervals, were seen in a repeat dose safety pharmacology study in monkeys at maximal plasma concentrations 8.9-fold greater than the concentrations obtained at therapeutic doses in humans with 300 mg intravenous infusion administration. Echocardiography revealed no indication of cardiac decompensation in a repeat dose safety pharmacology study in rats at a systemic exposure 2.2-fold greater than that achieved therapeutically. Increased systolic and arterial blood pressures (up to 29 mm-Hg) were seen in rats and monkeys at systemic exposures 2.2-fold and 8.9-fold greater, respectively, than those achieved with the human therapeutic doses.

A non-dose related incidence of thrombus/emboli in the lung was seen in the 1 month repeated dose study in the monkey. The clinical significance of this finding is unknown.

Reproduction, peri- and postnatal development studies were conducted in rats. At exposures lower than those obtained at therapeutic doses in humans, posaconazole caused skeletal variations and malformations, dystocia, increased length of gestation, reduced mean litter size and postnatal viability. In rabbits, posaconazole was embryotoxic at exposures greater than those obtained at therapeutic doses. As observed with other azole antifungal agents, these effects on reproduction were considered to be due to a treatment-related effect on steroidogenesis.

Posaconazole was not genotoxic in *in vitro* and *in vivo* studies. Carcinogenicity studies did not reveal special hazards for humans.

In a nonclinical study using intravenous administration of posaconazole in very young dogs (dosed from 2-8 weeks of age) an increase in the incidence of brain ventricle enlargement was observed in treated animals as compared with concurrent control animals. No difference in the incidence of brain ventricle enlargement between control and treated animals was observed following the subsequent 5-month treatment-free period. There were no neurologic, behavioural or developmental abnormalities in the dogs with this finding, and a similar brain finding was not seen with oral posaconazole administration to juvenile dogs (4 days to 9 months of age) or intravenous posaconazole administration to juvenile dogs (10 weeks to 23 weeks of age). The clinical significance of this finding is unknown.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Betadex Sulfobutyl Ether Sodium (SBECD)
Disodium edetate
Hydrochloric acid [for pH adjustment]
Sodium hydroxide [for pH adjustment]
Water for injections

6.2 Incompatibilities

Posaconazole 300 mg must not be diluted with:
- Lactated Ringer’s solution
- 5 % dextrose with Lactated Ringer’s solution
- 4.2 % sodium bicarbonate

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

30 months

Chemical and physical in-use stability has been demonstrated for 24 hours at 25°C. From a microbiological point of view, once admixed, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8ºC, unless reconstitution/dilution has taken place in controlled and validated aseptic conditions. This medicinal product is for single use only.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

For storage conditions after dilution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Amber type I glass vial of 20 ml closed with bromobutyl rubber stopper and aluminium seal containing 16.7 mL of solution.
Pack size: 1 vial

6.6 Special precautions for disposal

Administration instructions for Posaconazole 300 mg concentrate for solution for infusion

- Aseptically transfer 16.7 ml of posaconazole to an intravenous bag (or bottle) containing a compatible admixture diluent (see below for list of diluents) using the volume ranging from 150 mL to 283 mL depending on the final concentration to be achieved (not less than 1 mg/ml and not greater than 2 mg/ml).
- Administer via a central venous line, including a central venous catheter or peripherally inserted central catheter (PICC) by slow intravenous infusion over approximately 90 minutes. Posaconazole 300 mg concentrate for solution for infusion should not be given by bolus administration.
- If a central venous catheter is not available, a single infusion may be administered through a peripheral venous catheter with a volume to achieve a dilution of approximately 2 mg/ml. When administered through a peripheral venous catheter, the infusion should be administered over approximately 30 minutes.
  Note: In clinical trials, multiple peripheral infusions given through the same vein resulted in infusion site reactions (see section 4.8).
- Posaconazole 300 mg is for single use.

The following medicinal products can be infused at the same time through the same intravenous line (or cannula) as Posaconazole 300 mg concentrate for solution for infusion:

Ciprofloxacin
Daptomycin
Gentamicin sulfate
Levofloxacin
Morphine sulphate
Norepinephrine
Potassium chloride

Any products not listed in the table above should not be coadministered with Posaconazole 300 mg through the same intravenous line (or cannula).

Posaconazole 300 mg concentrate for solution for infusion should be inspected visually for particulate matter prior to administration. The solution of Posaconazole 300 mg

ranges from colourless to slightly yellow. Variations of colour within this range do not affect the quality of the product.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Posaconazole 300 mg must not be diluted with:

Lactated Ringer's solution
5 % dextrose with Lactated Ringer's solution
4.2 % sodium bicarbonate

This medicinal product must not be mixed with other medicinal products except those mentioned below:

5 % dextrose in water
0.9 % sodium chloride
0.45 % sodium chloride
5 % dextrose and 0.45 % sodium chloride
5 % dextrose and 0.9 % sodium chloride
5 % dextrose and 20 mEq KCl

7 MARKETING AUTHORISATION HOLDER

Altan Pharma Ltd
Lennox Building, 50 South Richmond street
Dublin 2, D02FK02, Ireland

8 MARKETING AUTHORISATION NUMBER(S)

PL 46788/0031

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

12/11/2021

10 DATE OF REVISION OF THE TEXT

02/05/2025