SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT
FUGAFYL 40 mg/ml Oral Suspension

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Each ml suspension contains:
Active Substance(s):
Posaconazole_____40 mg
Excipient(s) with known effect:
Glucose (liquid)_____350 mg
Propylene glycol_____2.87 mg
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM
Oral suspension.
White to off-white homogenous suspension free from foreign matter with characteristic odour.

4. CLINICAL PARTICULARS
4.1 Therapeutic indications
FUGAFYL is indicated for use in treating the following fungal infections in adults (see section 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;
- Oropharyngeal candidiasis: as first-line therapy in patients who have severe disease or are immunocompromised, in whom response to topical therapy is expected to be poor.

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.

FUGAFYL is also indicated for prophylaxis of invasive fungal infections in the following patients:
- Patients on chemotherapy for induction of remission of acute myeloblastic leukemia (AML) or myelodysplastic syndromes (MDS) for which prolonged neutropenia is expected and who are at high risk of developing invasive fungal infections;
- Subjects undergoing hematopoietic stem cell transplantation (HSCT) in high-dose immunosuppressive therapy for graft-versus-host disease and who are at high risk of developing invasive fungal infections.

4.2 Posology and method of administration
Non-interchangeability between posaconazole tablets and FUGAFYL oral suspension
Treatment should be initiated by a physician experienced in the treatment of fungal infections or supportive therapy in high-risk patients for whom prophylaxis with posaconazole is indicated.

Non-interchangeability between posaconazole tablets and FUGAFYL oral suspension:
FUGAFYL oral suspension is indicated for the adult population (≥18 years old) only.

The tablet and oral suspension should not be used interchangeably due to the differences between these two formulations in the frequency of administration, administration with food and plasma drug concentration that is achieved. Therefore, follow the specific dosing recommendations for each formulation.

Posology
Posaconazole is also available as a 100 mg gastro-resistant tablet and in 300 mg concentrate for solution for infusion. Posaconazole tablets are the preferred formulation for optimizing plasma concentrations and generally provide higher plasma exposures to the drug than FUGAFYL oral suspension under both fed and fasted conditions.

Frequency and duration of administration
The recommended dose is indicated in Table 1.

Table 1. Recommended dose in adults according to indication

Indication	Dose and duration of therapy
Refractory invasive fungal infections (IFI) / 1st line treatment of patients with invasive fungal infections intolerant to other antifungal therapies	200 mg (5 mL) 4 times a day. In patients who cannot tolerate food or a nutritional supplement, FUGAFYL should be administered at a dose of 400 mg (10 mL) twice daily. Duration of therapy should be based on the severity of the underlying disease, recovery from immunosuppression and clinical response.
Coccidioidomycosis	200 mg (5 mL) 4 times a day. In patients who cannot tolerate food or a nutritional supplement, FUGAFYL should be administered at a dose of 400 mg (10 mL) twice daily. Duration of therapy should be based on the severity of the underlying disease, recovery from immunosuppression and clinical response.
Oropharyngeal candidiasis	Loading dose of 200 mg (5 mL) once a day on the first day, then 100 mg (2.5 mL) once a day for 13 days. Each dose of FUGAFYL should be administered during or immediately after a meal, or a nutritional supplement in patients who cannot tolerate food to enhance the oral absorption and to ensure adequate exposure.
Refractory oropharyngeal candidiasis	400 mg (10 mL) twice a day. Duration of therapy should be based on the severity of the underlying disease and clinical response.
Prophylaxis of invasive fungal infections	200 mg (5 mL) 3 times a day. Each dose of FUGAFYL should be administered during or immediately after food or food supplement intake, in patients who cannot tolerate food, to increase oral absorption and ensure adequate exposure to the medicinal product. The duration of therapy is based on recovery from neutropenia or immunosuppression. For patients with acute myeloid leukemia or myelodysplastic syndrome, prophylaxis with FUGAFYL 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.

Method of administration
For oral use. The recommended dose is shown in Table 1. FUGAFYL should be given with meals or 240 mL of nutritional supplements. It should be taken with meals or within 20 minutes immediately after meals. The oral suspension should be shaken well before use.

Additional information on special populations
Renal impairment
No effect of renal impairment on the pharmacokinetics of posaconazole is expected and no dose adjustment is recommended (see section 5.2).

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.

Pediatric population
The safety and efficacy of posaconazole oral suspension have not been established in children and adolescents aged below 18 years. Therefore, the use of FUGAFYL in patients under 18 years of age is not recommended (see sections 5.1 and 5.2).

Geriatric population
The safety profile of posaconazole was similar in the elderly and the young in clinical efficacy studies.

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 Leukemia (CLL) patients (see sections 4.4 and 4.5).

4.4 Special warnings and precautions for use
Hypersensitivity
There is no data on cross-sensitivity between posaconazole and other azole antifungal agents. Caution should be used when prescribing posaconazole to patients with hypersensitivity to other azoles.

Hepatic toxicity
Hepatic reactions (e.g. mild to moderate 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 normalized 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 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 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 should be considered if clinical signs and symptoms are consistent with development of liver disease.

QTc prolongation
Some azoles are known to be associated with prolongation of the QTc interval. Posaconazole 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 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 disorders, particularly those involving potassium, magnesium or calcium levels, should be monitored and corrected if necessary before and during FUGAFYL therapy.

Drug interactions
Posaconazole is an inhibitor of CYP3A4 and should only be used in particular situations during treatment with other medicinal products that are metabolized by CYP3A4 (see section 4.5).

Midazolam and other benzodiazepines metabolized by CYP3A4
Due to the risk of prolonged sedation and possible respiratory depression co-administration of posaconazole with any benzodiazepines metabolized by CYP3A4 (e.g. midazolam, triazolam, alprazolam) should only be considered if clearly necessary. Dose adjustment of benzodiazepines metabolized 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. Azole antifungals, including posaconazole, should be reserved 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 tumor lysis syndrome (TLS) and neutropenia (see sections 4.3 and 4.5). Refer to the venetoclax SPC for detailed guidance.

Rifamycin antibacterials (rifampicin, rifabutin), certain anticonvulsants (phenytoin, carbamazepine, phenobarbital, primidone), efavirenz and cimetidine
Posaconazole concentrations may be significantly reduced in combination; for this reason,

concomitant use with posaconazole should be avoided unless the benefit to the patient outweighs the risk (see section 4.5).

Gastrointestinal dysfunction
There are limited pharmacokinetic data in patients with severe gastrointestinal dysfunction (such as severe diarrhea). Patients who have severe diarrhea or vomiting should be monitored closely for breakthrough fungal infections.

This medicinal product contains approximately 1.75 g of glucose per 5 ml of suspension. This should be taken into account in diabetic patients. Patients with rare glucose-galactose malabsorption should not take this medicine.

This medicinal product contains 14.35 propylene glycol per 5 mL of suspension.

4.5 Interaction with other medicinal products and other forms of interaction

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

H_2 receptor antagonists and proton pump inhibitors
Posaconazole plasma concentrations (C_{max} and AUC) were reduced by 39% when posaconazole was administered with cimetidine (400 mg twice a day) due to reduced absorption possibly secondary to

a decrease in gastric acid production. Co-administration of posaconazole with H_2 receptor antagonists should be avoided if possible.

Similarly, administration of 400 mg posaconazole with esomeprazole (40 mg daily) decreased mean C_{max} and AUC by 46% and 32%, respectively, compared to dosing with 400 mg posaconazole alone. Co-administration of posaconazole with proton pump inhibitors should be avoided if possible.

Food: The absorption of posaconazole is significantly increased by food (see sections 4.2 and 5.2).

Effects of posaconazole on other medicinal products
Posaconazole is a potent inhibitor of CYP3A4. Co-administration of posaconazole with CYP3A4 substrates which are administered intravenously 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. The effect of posaconazole on the plasma concentrations of orally administered CYP3A4 substrates is unknown, but a greater effect can be expected than with intravenously administered substrates. 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. Several of the interaction studies were conducted in healthy volunteers in whom a higher exposure to posaconazole occurs compared to patients administered the same dose. The effect of posaconazole on CYP3A4 substrates in patients might be somewhat lower than that observed in healthy volunteers, and is expected to be variable between patients due to the variable posaconazole exposure in patients. The effect of co-administration with posaconazole on plasma levels of CYP3A4 substrates may also be variable within a patient, unless posaconazole is administered in a strictly standardized way with food, given the large food effect on posaconazole exposure (see section 5.2).

Terfenadine, astemizole, cisapride, pimozide, halofantrine and quinidine (CYP3A4 substrates)
Co-administration of posaconazole and terfenadine, astemizole, cisapride, pimozide, halofantrine and 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 metabolized through CYP3A4 (e.g. simvastatin, lovastatin and atorvastatin)
Posaconazole may substantially increase plasma levels of HMG-CoA reductase inhibitors that are metabolized 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, azole

antifungals, including posaconazole, should be reserved for patients receiving a vinca alkaloid, including vincristine, who have no alternative antifungal treatment options.

Rifabutin
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 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 and inadequate treatment. 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 hospitalization 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. 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 metabolized 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 0.4 mg single dose of intravenous midazolam 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 single dose of 2 mg midazolam by 2.2 and 4.5-fold, respectively. In addition, 200 mg or 400 mg posaconazole oral suspension 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 given together with any benzodiazepine that is metabolized by CYP3A4 (e.g. midazolam, triazolam, alprazolam) (see section 4.4).

Calcium channel blockers metabolized 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
Co-administration of other azoles with digoxin is known to cause increased levels of digoxin. 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 metabolized 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 hypercalcemia). 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 C_{max} 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 SPC.

Additional information on special populations

Pediatric population
Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and lactation
General advice
Pregnancy category "C".

Women of child-bearing potential / Contraception
Women of child-bearing potential have to use effective contraception during treatment. FUGAFYL interacts with oral contraceptives. Therefore, an effective and reliable method of contraception should be used during treatment.

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. FUGAFYL should not be used during pregnancy unless necessary. Posaconazole must not be used during pregnancy unless the benefit to the mother clearly outweighs the potential risk to the fetus.

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.

Reproduction ability / Fertility
Posaconazole had no effect on fertility of male rats at doses up to 180 mg/kg (1.7 times the 400-mg twice daily regimen based on steady-state plasma concentrations in healthy volunteers) or female rats at a dose up to 45 mg/kg (2.2 times the 400-mg twice daily regimen). 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 some adverse reactions (e.g. dizziness, somnolence, etc.) which may potentially affect the ability to drive/use machines have been reported with the use of posaconazole, caution is necessary.

4.8 Undesirable effects
Summary of the safety profile
Safety of posaconazole oral suspension has been assessed in >2,400 patients and healthy volunteers enrolled in clinical trials and from post-marketing experience. The most frequently reported serious related adverse reactions included nausea, vomiting, diarrhea, pyrexia, and increased bilirubin.

Tabulated list of adverse reactions
Within the system organ class, adverse reactions are listed by 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 available data).

Table 2. Adverse reactions by body system and frequency reported in clinical trials and/or post-marketing use* (based on adverse reactions observed with oral suspension, enteric tablets, and concentrate for solution for infusion.)

Blood and lymphatic system disorders

Common	Neutropenia
Uncommon	Thrombocytopenia, leukopenia, anemia, eosinophilia, lymphadenopathy, splenic infarction
Rare	Hemolytic uremic syndrome, thrombotic thrombocytopenic purpura, pancytopenia, coagulopathy, hemorrhage
Immune system disorders	
Uncommon	Allergic reaction
Rare	Hypersensitivity reaction
Endocrine disorders	
Rare	Adrenal insufficiency, blood gonadotropin decreased, pseudoaldosteronism
Metabolism and nutrition disorders	
Common	Electrolyte imbalance, anorexia, decreased appetite, hypomagnesaemia, hypokalemia
Uncommon	Hyperglycemia, hypoglycemia
Psychiatric disorders	
Uncommon	Abnormal dreams, confusional state, sleep disorder
Rare	Psychotic disorder, depression
Nervous system disorders	
Common	Paresthesia, dizziness, somnolence, headache, dysgeusia
Uncommon	Convulsions, neuropathy, hypoesthesia, tremor, aphasia, insomnia
Rare	Cerebrovascular accident, encephalopathy, peripheral neuropathy, syncope
Eye disorders	
Uncommon	Blurred vision, photophobia, visual acuity reduced
Rare	Diplopia, scotoma
Ear and labyrinth disorder	
Rare	Hearing impairment
Cardiac disorders	
Uncommon	Long QT syndrome[§], electrocardiogram abnormal[§], palpitations, bradycardia, supraventricular extrasystoles, tachycardia
Rare	Torsade de pointes, sudden death, ventricular tachycardia, cardio-respiratory arrest, cardiac failure, myocardial infarction
Vascular disorders	
Common	Hypertension
Uncommon	Hypotension, vasculitis
Rare	Pulmonary embolism, deep vein thrombosis
Respiratory, thoracic and mediastinal disorders	
Uncommon	Cough, epistaxis, hiccups, nasal congestion, pleuritic pain, tachypnea
Rare	Pulmonary hypertension, interstitial pneumonia, pneumonitis
Gastrointestinal disorders	
Very common	Nausea
Common	Vomiting, abdominal pain, diarrhea, dyspepsia, dry mouth, flatulence, anorectal discomfort, constipation
Uncommon	Pancreatitis, abdominal distension, enteritis, epigastric discomfort, eructation, gastro-esophageal reflux disease, edema mouth
Rare	Gastrointestinal hemorrhage, ileus
Hepatobiliary disorders	
Common	Liver function tests raised (ALT increased, AST increased, bilirubin increased, alkaline phosphatase increased, GGT increased)
Uncommon	Hepatocellular damage, hepatitis, jaundice, hepatomegaly, cholestasis, hepatic toxicity, hepatic function abnormal
Rare	Hepatic failure, hepatitis cholestatic, hepatosplenomegaly, liver tenderness, asterixis
Skin and subcutaneous tissue disorders	

Common	Rash, pruritus
Uncommon	Mouth ulceration, alopecia, dermatitis, erythema, petechiae
Rare	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	Acute renal failure, renal failure, blood creatinine increased
Rare	Renal tubular acidosis, interstitial nephritis
Reproductive system and breast disorders	
Uncommon	Menstrual disorder
Rare	Breast pain
General disorders and administration site conditions	
Common	Fever, asthenia, fatigue
Uncommon	Edema, pain, chills, malaise, chest discomfort, drug intolerance, feeling jittery, mucosal inflammation
Rare	Tongue edema, face edema
Investigations	
Uncommon	Altered medicine levels, blood phosphorus decreased, chest x-ray abnormal

* Based on adverse reactions observed with the oral suspension, gastro-resistant tablets, concentrate for solution for infusion, and gastro-resistant powder and solvent for oral suspension.
§ See section 4.4.

Description of selected adverse reactions
Hepatobiliary disorders
Severe hepatic impairment with fatal outcome was reported during post-marketing monitoring of posaconazole oral suspension (see section 4.4).

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorization 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 national reporting system.

4.9 Overdose
During clinical trials, patients who received posaconazole oral suspension at doses up to 1,600 mg/day had no adverse reactions other than those reported with patients treated at lower doses.
Accidental overdose was observed in a patient who had taken posaconazole oral suspension 1,200 mg twice daily for three days. No adverse reactions were noted by the investigator.
Posaconazole is not eliminated by hemodialysis. Special treatment is not available in case of overdose with posaconazole. Supportive care can be considered.

5. PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
Pharmacotherapeutic group : Antimycotics for systemic use, triazole derivatives
ATC code : J02AC04

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 (*Candida 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
Isolated clinical strains with decreased susceptibility to posaconazole have been identified. The main 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 (The European Committee on Antimicrobial Susceptibility Testing) methodology.

EUCAST ECOFF values:
- *Aspergillus flavus* : 0.5 mg/L
- *Aspergillus fumigatus* : 0.5 mg/L
- *Aspergillus nidulans* : 0.5 mg/L
- *Aspergillus niger* : 0.5 mg/L
- *Aspergillus terreus* : 0.25 mg/L

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

Breakpoints
EUCAST (The European Committee on Antimicrobial Susceptibility Testing) minimum inhibitory concentration (MIC) breakpoints for posaconazole [susceptible (S); resistant (R)]:

- *Candida albicans* : S ≤0.06 mg/L, R >0.06 mg/L
- *Candida tropicalis* : S ≤0.06 mg/L, R >0.06 mg/L
- *Candida parapsilosis* : S ≤0.06 mg/L, R >0.06 mg/L
- *Candida dubliniensis* : S ≤0.06 mg/L, R > 0.06 mg/L

There are currently insufficient data to set clinical breakpoints for other *Candida* species.

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.

Pharmacokinetic / Pharmacodynamic relationships
The ratio of total exposure to minimum inhibitory concentration (AUC/MIC) to the medicinal product has been observed to correlate with clinical outcome. 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 and the effects of food on absorption).

Clinical experience

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 (Study 0041). 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 3, 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, randomized controlled study and so all comparisons with the external control group should be viewed with caution.

Table 3. Overall efficacy of posaconazole oral suspension at the end of treatment for invasive aspergillosis in comparison to an external control group

	Posaconazole		Control group	
Overall Response	45/107 (42%)		22/86 (26%)	
Success by species				
Aspergillus spp.*	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%)

* 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.

Treatment of azole-susceptible Oropharyngeal Candidiasis

A randomized, evaluator-blind, controlled study was completed in HIV-infected patients with azole-susceptible oropharyngeal candidiasis (most patients studied had *C. albicans* isolated at baseline).

The primary efficacy variable was the clinical success rate (defined as cure or improvement) after 14 days of treatment. Patients were treated with posaconazole or fluconazole oral suspension (both posaconazole and fluconazole were given as follows: 100 mg twice a day for 1 day followed by 100 mg once a day for 13 days).

The clinical response rates from the above study are shown in the Table 4 below.
Posaconazole was shown to be non-inferior to fluconazole for clinical success rates at Day 14 as well as 4 weeks after the end of treatment.

Table 4. Clinical success rates in Oropharyngeal Candidiasis

Endpoint	Posaconazole	Fluconazole
Clinical success rate at Day 14	91.7% (155/169)	92.5% (148/160)
Clinical success rate 4 weeks after end of treatment	68.5% (98/143)	61.8% (84/136)

Clinical success rate was defined as the number of cases assessed as having a clinical response (cure or improvement) divided by the total number of cases eligible for analysis.

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

Study 316 was a randomized, 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-randomization 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 randomized, 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 leukemia 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-randomization. New diagnosis of acute myelogenous leukemia 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 5 and 6 for results from both studies.

There were fewer breakthrough *Aspergillus* infections in patients receiving posaconazole prophylaxis when compared to control patients.

Table 5. 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)	0.074

FLU = fluconazole; ITZ = itraconazole; POS = posaconazole.
[a]: FLU/ITZ (1899); FLU (316).
[b]: In 1899 this was the period from randomization 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 randomization to 100 days post-randomization; in 316 it was the period from the baseline day to 111 days post-baseline.
[d]: All randomized
[e]: All treated

Table 6. 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 randomization 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 randomization to 100 days post-randomisation; in 316 it was the period from the baseline day to 111 days post-baseline.
d: All randomized
e: All treated

In Study 1899, a significant decrease in all-cause mortality in favor 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 randomization, 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).

Use in pediatric population
No dose of posaconazole oral suspension could be recommended for pediatric patients. However, the safety and efficacy of other formulations of posaconazole have been established in pediatric patients 2 to less than 18 years of age. Refer to their SPC for additional information.

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

General characteristics

Absorption
Posaconazole is absorbed with a median t_{max} of 3 hours (fed patients). The pharmacokinetics of posaconazole are linear following single and multiple dose administration of up to 800 mg when taken with a high fat meal. No further increases in exposure were observed when doses above 800 mg daily were administered to patients and healthy volunteers. In the fasting state, AUC increased less than in proportion to dose above 200 mg. In healthy volunteers under fasting conditions, dividing the total daily dose (800 mg) into 200 mg four times daily compared to 400 mg twice daily, was shown to increase posaconazole exposure by 2.6-fold.

Effect of food on oral absorption in healthy volunteers
The absorption of posaconazole was significantly increased when posaconazole 400 mg (once daily) was administered during and immediately after the consumption of a high fat meal (~50 g fat) compared to administration before a meal, with C_{max} and AUC increasing by approximately 330% and 360%, respectively. The AUC of posaconazole is: 4 times greater when administered with a high-fat meal (~50 g fat) and about 2.6 times greater when administered during a non-fat meal or nutritional supplement (14 g fat) relative to the fasted state (see sections 4.2 and 4.5).

Distribution
Posaconazole is slowly absorbed and slowly eliminated with a large apparent volume of distribution (1,774 liters) and is highly protein bound (> 98%), predominantly to serum albumin.

Biotransformation
Posaconazole does not have any major circulating metabolites and its concentrations are unlikely to be altered by inhibitors of CYP450 enzymes. 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 feces account for approximately 17% of the administered radiolabeled dose.

Elimination
Posaconazole is slowly eliminated with a mean half-life ($t_{1/2}$) of 35 hours (range 20 to 66 hours). After administration of ^{14}C-posaconazole, radioactivity was predominantly recovered in the feces (77% of the radiolabeled dose) with the major component being parent compound (66% of the radiolabeled dose). Renal clearance is a minor elimination pathway, with 14% of the radiolabeled dose excreted

in urine (< 0.2% of the radiolabeled dose is parent compound). Steady-state is attained following 7 to 10 days of multiple-dose administration.

Linearity / Nonlinearity
The pharmacokinetics of posaconazole are linear following single and multiple dosing up to 800 mg when taken with high fat food.

Pharmacokinetics in special populations
Children (<18 years)
Following administration of 800 mg per day of posaconazole as a divided dose for treatment of invasive fungal infections, mean trough plasma concentrations from 12 patients 8 - 17 years of age (776 ng/mL) were similar to concentrations from 194 patients 18 - 64 years of age (817 ng/mL). Similarly, in the prophylaxis studies, the mean steady-state posaconazole average concentration (C_{av}) was comparable among ten adolescents (13-17 years of age) to C_{av} achieved in adults (≥ 18 years of age). In a study of 136 neutropenic pediatric patients 11 months – 17 years treated with posaconazole oral suspension at doses up to 18 mg/kg/day divided TID, approximately 50% met the pre-specified target (Day 7 C_{av} between 500 ng/ml-2,500 ng/ml). In general, exposures tended to be higher in the older patients (7 to <18 years) than in younger patients (2 to <7 years).

Gender
The pharmacokinetics of posaconazole are comparable in men and women.

Elderly
An increase in C_{max} (26%) and AUC (29%) was observed in elderly subjects (24 subjects ≥ 65 years of age) relative to younger subjects (24 subjects 18 - 45 years of age). However, in clinical efficacy trials, the safety profile of posaconazole between the young and elderly patients was similar.

Race
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 C_{av} is decreased by 25% and in patients < 50 kg, the C_{av} 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} ≥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 hemodialysis. Because of the variability in exposure, patients with severe renal impairment should be closely monitored for fungal infections occurring under treatment/prophylaxis (see sections 4.4 and 5.2).

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, 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.

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 systemic exposures 4.6-fold greater than the concentrations obtained at therapeutic doses in humans. Echocardiography revealed no indication of cardiac decompensation in a repeat dose safety pharmacology study in rats at a systemic exposure 1.4-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 1.4-fold and 4.6-fold greater, respectively, than those achieved with the human therapeutic doses.

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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Glucose (liquid)
Polysorbate 80
Xanthan gum
Sodium benzoate
Citric acid monohydrate

Sodium citrate dihydrate
Glycerin
Titanium dioxide
Simethicone emulsion 30% (Q7-2587)
Cherry flavor containing propylene glycol
Purified water

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
36 months.

6.4 Special precautions for storage
Store at room temperature below 25°C. After the product is opened, it should be stored at 25°C (without freezing) and used within 28 days.

6.5 Nature and contents of container
The primary packaging material of FUGAFYL 40 mg/ml Oral Suspension is a 28 pp honey-colored Type III glass bottle containing 105 mL suspension and a white-colored child-proof 28 mm polypropylene cap. Each cardboard box includes a glass bottle, a 5 mL transparent measuring spoon with 2.5 mL and 5 mL lines, and a package leaflet.

6.6 Special precautions for disposal and other handling
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORIZATION HOLDER
DEVA Holding A.Ş.
Halkalı Merkez Mah. Basın Ekspres Cad. No: 1
34303 Küçükçekmece – İSTANBUL / TÜRKİYE

8. MARKETING AUTHORIZATION NUMBER
2021/57

9. DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION
Date of first authorization : 18.03.2021
Date of latest renewal :

10. DATE OF REVISION OF THE TEXT
13.06.2024