

THINK FLT3
ONE MORE TIME



AML: DEVASTATING

IN PATIENTS WITH AML,
**A FLT3-ITD mutation drives
progression and may lead to
lower patient survival.¹⁻³**

WITH A FLT3
MUTATION: **DISASTROUS**



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Prescribing information for: XOSPATA™ 120mg film coated tablets (gilteritinib). **Indications:** Gilteritinib is indicated as monotherapy for the treatment of adult patients who have relapsed or refractory acute myeloid leukaemia (AML) with a FLT3 mutation. **Posology and administration:** Treatment with gilteritinib should be initiated and supervised by a physician experienced in the use of anti-cancer therapies. Before taking gilteritinib, relapsed or refractory AML patients must have confirmation of FMS-like tyrosine kinase 3 (FLT3) mutation (internal tandem duplication [ITD] or tyrosine kinase domain [TKD]) using a validated test. The recommended starting dose is 120 mg gilteritinib (three 40 mg tablets) orally once daily, with or without food, swallowed whole with water and should not be broken or crushed. Gilteritinib should be administered at about the same time each day. See Special warnings and precautions for use section on tests to be conducted prior to initiation e.g. blood chemistry, ECG and pregnancy test. Treatment should continue until the patient is no longer clinically benefiting from gilteritinib or until unacceptable toxicity occurs. Response may be delayed; therefore, continuation of treatment at the prescribed dose for up to 6 months should be considered to allow time for a clinical response. In the absence of a response (patient did not achieve a complete remission [CR] after 4 weeks of treatment), the dose can be increased to 200 mg (five 40 mg tablets) once daily, if tolerated or clinically warranted. Gilteritinib may be re-initiated in patients following haematopoietic stem cell transplantation (HSCT). **Planned HSCT:** Interrupt treatment one week prior to administration of the conditioning regimen. **HSCT treatment:** HSCT treatment should be resumed once the patient has achieved a complete remission (CR) after 22 cycles of treatment with CR. **Elderly:** No dose adjustment is required in patients ≥65 years of age. Gilteritinib is not recommended for use in patients with severe (Child-Pugh Class C) hepatic impairment. Please refer to SPC, section 4.2 for full instructions for use in hepatic & renal impairment. **Paediatric population:** The safety and efficacy of gilteritinib in children aged below 18 years has not yet been established. No data are available. Due to in vitro binding to 5HT_{2A}, there is a potential impact on cardiac development in patients less than 6 months of age. **Contraindications:** Hypersensitivity to the active substance or to any of the excipients listed in section 6.1 of the SPC. **Special warnings and precautions for use:** Differentiation syndrome: Gilteritinib has been associated with differentiation syndrome. Differentiation syndrome is associated with rapid proliferation and differentiation of myeloid cells and may be life-threatening or fatal if not treated. Symptoms and clinical findings of differentiation syndrome include fever, dyspnoea, pleural effusion, pericardial effusion, pulmonary oedema, hypotension, rapid weight gain, peripheral oedema, rash, and renal dysfunction. If differentiation syndrome is suspected, corticosteroid therapy should be initiated along with haemodynamic monitoring until symptom resolution. If severe signs and/or symptoms persist for more than 48 hours after initiation of corticosteroids, gilteritinib should be interrupted until signs and symptoms are no longer severe. Corticosteroids can be tapered after resolution of symptoms and should be administered for a minimum of 10 days. **Reversible encephalopathy syndrome:** Signs and symptoms of PRES (PRES is a form of reversible encephalopathy syndrome) have been reported in patients receiving gilteritinib. PRES has been reported in patients with reversible encephalopathy syndrome. PRES is a rare, reversible, neurological disorder which can present with rapidly evolving symptoms including seizure, headache, confusion, visual and neurological disturbances, with or without associated hypertension and altered mental status. If PRES is suspected, it should be confirmed by brain imaging, preferably magnetic resonance imaging (MRI). Discontinuation of gilteritinib in patients who develop PRES is recommended. Prolonged QT interval: Gilteritinib has been associated with prolonged cardiac ventricular repolarisation (QT interval). QT prolongation can be observed in the first three months of treatment with gilteritinib. Therefore, ECG should be performed prior to initiation of treatment, on day 8 and 15 of cycle 1, and prior to the start of the next three subsequent months of treatment. Caution is warranted in patients with relevant cardiac history. Hypokalaemia or hypomagnesaemia may increase the QT prolongation risk. Hypokalaemia or hypomagnesaemia should therefore be corrected prior to and during gilteritinib treatment. Gilteritinib should be interrupted in patients who have a QTcF >500 msec. The decision to re-introduce gilteritinib treatment after an event of QT prolongation should be based on careful consideration of benefits and risks. Resume gilteritinib at a reduced dose (from 120 mg to 80 mg or from 200 mg to 120 mg) when QTcF is ≤500 msec. Patients with QTcF ≤500 msec should be monitored for QTcF. If QTcF is >500 msec, the dose should be reduced to 80 mg. If gilteritinib is re-introduced at a reduced dose, ECG should be performed after 15 days of dosing, and prior to the start of the next three subsequent months of treatment. In clinical studies, 12 patients had pancreatitis. There have been reports of pancreatitis. Patients who develop signs and symptoms suggestive of pancreatitis should be evaluated and monitored. Gilteritinib should be interrupted and can be resumed at a reduced dose (reduced from 120 mg to 80 mg or from 200 mg to 120 mg) when the signs and symptoms of pancreatitis have resolved. **Toxicity:** If the patient experiences other Grade 3 or higher toxicity considered related to treatment, interrupt

treatment until the toxicity resolves or improves to Grade 1. If deemed clinically appropriate gilteritinib can be resumed at a reduced dose (reduced from 120 mg to 80 mg or from 200 mg to 120 mg). **Interactions:** Co-administration of CYP3A4/P-gp inducers may lead to decreased gilteritinib exposure and consequently a risk for lack of efficacy. Therefore, concomitant use of gilteritinib with strong CYP3A4/P-gp inducers should be avoided. Caution is required when concomitantly prescribing gilteritinib with medicinal products that are strong inhibitors of CYP3A4/P-gp and/or breast cancer resistant protein (BCRP) (such as, but not limited to, voriconazole, itraconazole, posaconazole and clarithromycin) because they can increase gilteritinib exposure. Alternative medicinal products that do not strongly inhibit CYP3A4, P-gp and/or BCRP activity should be considered. In situations where satisfactory therapeutic alternatives do not exist, patients should be closely monitored for toxicities during administration of gilteritinib. Gilteritinib may reduce the effects of medicinal products that target 5HT_{2A} receptor or sigma non-specific receptors. Therefore, concomitant use of gilteritinib with these products should be avoided unless use is considered essential for the care of the patient. **Embryofetal toxicity and contraception:** Pregnant women should be informed of the potential risk to a foetus. Females of reproductive potential should be advised to have a pregnancy test within seven days prior to starting treatment with gilteritinib and to use effective contraception during treatment with gilteritinib and for at least 6 months after stopping gilteritinib and to use effective hormonal contraceptives should add a barrier method of contraception. Males with female partners of reproductive potential should be advised to use effective contraception during treatment and for at least 4 months after the last dose of gilteritinib. **Interactions:** Gilteritinib is primarily metabolised by CYP3A4 enzymes, which are induced or inhibited by a number of concomitant drugs. See Special warnings and precautions for use section for further details on the effects of gilteritinib. Use of gilteritinib with strong CYP3A4/P-gp inducers or sigma non-specific receptors. Gilteritinib as an inhibitor or inducer of gilteritinib is not an inhibitor or inducer of CYP3A4 or an inhibitor of MATE1 in vivo. Gilteritinib is an inhibitor of P-gp, BCRP and OCT1 (organic cation transporter 1) in vitro. As no clinical data are available, it cannot be excluded that gilteritinib could inhibit these transporters at therapeutic doses. Caution is advised during co-administration of gilteritinib with substrates of P-gp (e.g., digoxin, dabigatran etexilate), BCRP (e.g., metoprolol, methotrexate, rosvastatin) and OCT1 (e.g., melatonin). **Fertility, pregnancy and lactation:** Pregnancy: Gilteritinib is not recommended during pregnancy and in women of childbearing potential not using effective contraception. See Special Warnings and Precautions for Use section above for information on pregnancy testing and contraception. **Breastfeeding:** Breastfeeding should be discontinued during treatment with gilteritinib and for at least two months after the last dose. **Fertility:** There are no data on the effect of gilteritinib on human fertility. **List of adverse reactions:** Prescribers should consult the SPC for full information on adverse events **List of adverse reactions:** Very common (≥1/10): Dizziness, Hypotension, Cough, Dyspnoea, Diarrhoea, Nausea, Constipation, Alanine aminotransferase increased, Aspartate aminotransferase increased, Blood creatine phosphokinase increased, Blood alkaline phosphatase increased, Pain in extremity, Arthralgia, Myalgia, Fatigue, Periorbital oedema and Asthenia. Common (≥1/10 to <1/10): Anaphylactic reaction, Electrocardiogram QT prolonged, Pericardial effusion, Pericarditis, Cardiac failure, Differentiation syndrome, Musculoskeletal pain, Acute kidney injury and Malaise. Serious adverse reactions: The most frequent serious adverse reactions noted from evaluation of 319 patients with gilteritinib were: fatal dyspnoea, fatal cardiac failure, fatal cardiac arrest, fatal myocardial infarction, fatal differentiation syndrome, fatal electrocardiogram QT prolonged and fatal reversible encephalopathy syndrome. **Overdose:** There is no known specific antidote for gilteritinib. In the event of an overdose, treatment should be stopped. Patients must be closely monitored for signs or symptoms of adverse reactions, and appropriate symptomatic and supportive treatment initiated, taking into consideration the long half-life estimated at 113 hours. **Cost (excluding VAT):** United Kingdom (UK): XOSPATA 40mg film-coated tablets x84: £14,188.00 **Legal classification:** POM. **Marketing authorisation number:** Great Britain (GB): PLGB 00166/0425, Northern Ireland (NI): EU/1/19/1399/001. **Marketing authorisation holder:** GB: Astellas Pharma Ltd., 300 Dashwood Lang Road, Bourne Business Park, Addlestone, United Kingdom, KT15 2NX, NI: Astellas Pharma Europe B.V., Sylvisweg 62, 2333 BE Leiden, The Netherlands. **Date of preparation:** March 2023. **Document number:** MAT_UK_XOS_2023_00039. **Further information available from:** Astellas Pharma Ltd., Medical Information: 0800 783 5018.

Adverse events should be reported. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store. Adverse events should also be reported to Astellas Pharma Ltd. on 0800 783 5018.

AML=acute myeloid leukaemia; FLT3=FMS-like tyrosine kinase 3; ITD=internal tandem duplication.

References: 1. Chevallier P, et al. Leukemia 2011;25(6):939-44. 2. Gale RE, et al. Blood 2008;111(5):2776-84. 3. Smith CC, et al. Nature 2012;485(7397):260-3.





Can you grow out of von Willebrand disease?

The problem of diagnosing von Willebrand disease (VWD) is well known and has spawned a proliferation of guidelines.¹⁻³ The problem relates mainly to the diagnosis of milder forms of type 1 VWD and their distinction from "low VWF" levels which may contribute to bleeding risk but not cause VWD.⁴ The question "can you grow out of VWD" arises from the well-known effect of increasing age on plasma levels of von Willebrand factor (VWF). Is this another diagnostic problem for VWD? One of the few benefits of growing older? Or is it a natural experiment giving insight into the relationship between VWF and haemostasis?

Inasmuch as VWD can be defined as a bleeding disorder arising from a deficiency of VWF haemostatic activity, this problem can be broken down into the following questions:

1. What is the effect of age on VWF?
2. What is the effect of age on bleeding?
3. How much VWF do you need for normal haemostasis?
4. Can the net effect of age reduce some patients' bleeding risk to within the normal range?

1 | THE EFFECT OF AGE ON VWF IN THE NORMAL POPULATION

Twin studies indicate that 60% of the population variation in VWF is genetic, one-third of which is attributable to ABO blood group, leaving a considerable amount attributable to acquired influences.⁵ A study by Gill of 1117 blood donors confirmed the effect of ABO group but noted that within blood groups the only significant correlation was a positive association with age.⁶ Several studies have confirmed that levels of VWF increase by approximately 10% per decade.⁷ The largest cross-sectional study, by Davies et al, measured VWF in 5052 blood donors in South Wales. This demonstrated a rise in VWF with age that was most marked after the age of 40.⁸ The rise was only 0.03 iu/mL between the third and fourth decade, increasing to 0.15 iu/mL between the sixth and seventh decade. However, Albanez et al have examined this in more detail and found that the effect of age was dependent on blood group. Although VWF in non-O individuals rose progressively with age, reaching a 1.71-fold rise in old age (mean 71±7, 55-87 years), the corresponding figure for group O was only 1.25. Interestingly, the well-documented ABO difference was barely evident in younger individuals but became more marked with age.⁹ Importantly, from a haemostatic point of view, the levels of Factor VIII remained closely correlated with VWF and showed largely parallel rises with age.

The mechanism underlying this rise is not fully known but appears to be multifactorial. Studies of VWF propeptide (VWFpp) have shown

that VWF secretion increases with age but again this is significant only in the oldest age group and only in non-O individuals.⁹ The reason for the increase in production with age is again not known but may reflect vascular damage or inflammation.¹⁰ There is an age-related rise in inflammatory mediators which may be responsible and blood group A has been linked to the development of atherosclerosis.¹¹ Despite the rise in secretion, the VWFpp:Ag ratio falls with age indicating an increase in half-life as well.^{9,12} This is consistent with the reported increase in FVIII half-life with age because FVIII survival is largely determined by VWF.¹³ The reduction in clearance is unexplained but once more is significantly more marked in the non-O group.

The net effect reported by Albanez was that non-O individuals can expect their VWF:Ag to rise from a mean of 0.98 to a mean of 1.68 iu/mL between childhood and old age, while group O rise from mean 0.85 to 1.11 iu/mL.⁹

2 | THE EFFECT OF AGE ON VWF IN PATIENTS WITH VWD

These well-documented changes describe the effect of age on VWF in the normal population but are unlikely to be reproduced in many patients with VWD. Clearly patients with type 3 VWD do not have the capacity to exhibit a rise under any circumstances and patients with significant defects in VWF synthesis (type 1 or type 2) are also unlikely to be able to produce rises of similar degree. In many patients with type 1 VWD, an increase in VWD clearance has been shown to be a contributory factor to the reduction in levels: this would tend to blunt any rise due to increased synthesis but may allow them to benefit from an age-related reduction in clearance, provided the normal physiological mechanisms are involved.¹⁴ Patients with type 2 variants may increase production, but any rise in activity is likely to be proportionately less.

Historically, many patients with VWF levels in the range 0.3-0.5 iu/mL have been diagnosed with VWD. Although this is now often regarded as "low VWF" (indicating that it is a risk factor that may contribute to, but not fully explain, a bleeding tendency)² these patients may have a positive bleeding history and might be in the best position to benefit from the age-associated VWF rise. Of note, approximately half of these patients do not have a variant in VWF and so are more likely to experience a rise similar to normals.¹⁵ On the other hand, they are also more frequently group O and so will experience a less marked rise than non-O individuals.

The WiN study comprised 664 patients with a diagnosis of VWD and historical level <0.3 iu/mL (activity or antigen).¹⁶ A subset of 66 patients had historical results for comparison over time. As expected,

no significant rise was seen in patients with type 2 VWD. In type 1 patients, the rise in VWF:Ag was 0.025 iu/mL per decade which as expected, is slightly less than seen in the normal population. The rise in VWF:RCO of 0.095 iu/mL per decade was slightly higher and although this is likely to be less accurate, it is interesting that ADAMTS13 levels fall with age; so some separation of antigen and function may be real.¹⁷ Indeed a study by Favaloro suggested a trend for the Ag: function ratio to fall with age, in keeping with this hypothesis.¹⁸ A Canadian study of patients with VWD documented a rise in mean VWF:Ag from 0.44 iu/mL to 0.71 iu/mL over a mean of 11 years follow-up. However, although in the group with baseline VWF:Ag <0.3 iu/mL the mean VWF:Ag rose from 0.23 to 0.57 iu/mL, only 2 of 8 patients had levels that rose from <0.3 to >0.5 iu/mL.¹⁹ This was a small study of 31 patients and it is not clear why the rises were higher than other studies.

In summary, the level of VWF rises significantly with age, but the effects are not surprisingly less marked in those with definite VWD (<0.3), the majority of whom will have a variant in VWF. Those with "low VWF" are better able to increase VWF with age but are most commonly blood group O whose age-related rise is less.

3 | BLEEDING AND AGE

Given that the incidence of many morbidities increases with age, it would not be surprising if there was a parallel increase in bleeding symptoms. In the European MCDMC study, Tosetto et al²⁰ found that bleeding score did indeed go up with age in patients with VWD, but not in the control group or unaffected family members. However, because the bleeding score is cumulative, this does not mean that bleeding became more common with age, only that it continued as the patients grew older. Nonetheless, some specific problems such as bleeding from angiodysplasia²¹ and haematuria²² are known to increase with age and age is an important component of a bleeding risk assessment tool for patients anticoagulated for atrial fibrillation.²³ For example, in the Leiden cohort, age >80 years compared to <60 years was associated with an adjusted hazard ratio for bleeding of 2.9 (95% CI: 1.7-4.8) despite similar quality of anticoagulant control.²⁴ Notably, the effect of age below 80 was not significant and this was also seen in the National Consortium of Anticoagulation Clinics study (RR for >80: 4.6 95% CI 1.2-18.1).²⁵ In the Inception Cohort study, the effect of age was a non-significant increasing trend but with an excess of fatal haemorrhage in the elderly.²⁶ In a web-based survey of younger, healthy individuals there was no increase in reported bleeding symptoms with age.²⁷

In the WIN study, elderly (>65 years) patients with VWD reported more bleeding episodes in the year preceding the study than younger patients: 42% vs 31% ($P=0.048$). Interestingly, this difference was entirely within the patients with type 2 disease and there was no difference for patients with type 1 VWD.¹⁶ Equally of note, the rise in VWF did not lead to a reduction in bleeding episodes in patients with type 1VWD. Elderly patients tended to bleed more frequently after surgery, had more GI bleeding and reported a higher number of

comorbidities. If the threshold VWF level for increased bleeding risk rose with age, then different criteria for diagnosis and treatment could be applied in this group.

In summary, there is little evidence for a general increase in bleeding associated with age independent of age-related comorbidities, but in patients with a bleeding diathesis such as VWD or anticoagulation, there may be an increase with advanced age.

4 | WHAT LEVEL OF VWF REPRESENTS A RETURN TO NORMAL BLEEDING RISK?

The question of whether a level of activity is low enough to cause or to explain bleeding is difficult. In the past many patients with levels below the lower limit of normal have been diagnosed with VWD on the basis of a reduced level alone or with coincidental symptoms but there are many individuals with levels <0.5 iu/mL who have no excessive bleeding tendency.⁴ The relative risk of bleeding for VWF:Ag below (vs above) 0.5 iu/mL is modest and of borderline significance: RR= 2.0 ($P=.51$).⁴ A similar result was obtained by Castaman et al who also noted that FVIII had a greater influence on the risk than VWF:Ag.²⁸ In the RENAWI study, the bleeding score began to rise only when the VWF:RCO fell below 0.3 iu/mL.²⁹ These data suggest that for patients with a significant bleeding history, a rise into the range 0.3-0.5 will likely reduce their bleeding risk and a rise to >0.5 will reduce it further but the possibility that other contributing risk factors are present means that it may not return entirely to normal.

Most patients with "low VWF" can be satisfactorily treated with desmopressin which will correct the primary haemostatic defect by elevating VWF and possibly sensitising platelets. In older patients, this approach may be contraindicated and the physician must decide whether a bleeding risk still exists and if so whether it is primarily due to an inadequate level of VWF or to another defect such as platelet dysfunction. It might be observed, for example, that PFA100 closure times remain prolonged despite a rise of VWF activity into the normal range. They may then be able to recommend either VWF or platelet replacement as prophylaxis against bleeding.

5 | CONCLUSION

Most patients with definite VWD will not experience a rise in VWF activity that normalizes their bleeding risk. However, those with less deleterious gene variants or low levels not linked to VWF, will experience a beneficial rise even if they do not achieve fully haemostatic levels. For some, whose VWF was in the borderline range, VWF may enter the normal range which will reduce their bleeding risk and may be sufficient to compensate for other contributory factors such as impaired platelet function; however, it is difficult to say they are growing out of VWD, since we are not certain of the initial diagnosis. Sadly, those with the most severe VWD will benefit the least. Explaining these changes to patients requires time and tact and the

question of growing out of VWD proves to be just as difficult to answer as making the diagnosis of VWD in general. In both cases, we are hampered by a lack of adequate data which will come only from large and long-term prospective studies of individuals both with and without VWD.

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