SUMMARY OF PRODUCT CHARACTERISTICS

1. NAMEOFTHEMEDICINALPRODUCT

Tasigna 50 mg hard capsules
Tasigna150mghardcapsules
Tasigna200mghardcapsules

2. QUALITATIVEANDQUANTITATIVECOMPOSITION

Tasigna50mghardcapsules

Onehardcapsulecontains50mgnilotinib(ashydrochloridemonohydrate).

Excipientwithknowneffect
Onehardcapsulecontains39.03mglactosemonohydrate.

Tasigna 150 mg hard capsules

Onehardcapsulecontains150mgnilotinib(ashydrochloridemonohydrate).

Excipientwithknowneffect
Onehardcapsulecontains117.08mglactosemonohydrate.

Tasigna 200 mg hard capsules

Onehardcapsulecontains200mgnilotinib(ashydrochloridemonohydrate).

Excipientwithknowneffect
Onehardcapsulecontains156.11mglactosemonohydrate. For

the full list of excipients, see section 6.1.

3. PHARMACEUTICALFORM

Hardcapsule.

Tasigna50mghardcapsules

Whitetoyellowishpowderinhardgelatincapsulewithredopaquecapandlightyellowopaquebody, size 4 with black radial imprint “NVR/ABL” on cap.

Tasigna150mghardcapsules

Whitetoyellowishpowderinredopaquehardgelatincapsules,size 1withblackaxialimprint “NVR/BCR”.

Tasigna200mghardcapsules

Whitetoyellowishpowderinlightyellowopaquehardgelatincapsules,size 0withredaxialimprint “NVR/TKI”.

4. CLINICALPARTICULARS

4.1 Therapeuticindications

Tasignaisindicatedforthetreatmentof:
- adultandpaediatricpatientswithnewlydiagnosedPhiladelphiachromosomepositivechronic myelogenous leukaemia (CML) in the chronic phase,
- adultpatientswithchronicphaseandacceleratedphasePhiladelphiachromosomepositiveCML with resistance or intolerance to prior therapy including imatinib. Efficacy data in patients with CML in blast crisis are not available,
- paediatricpatientswithchronicphasePhiladelphiachromosomepositiveCMLwithresistance or intolerance to prior therapy including imatinib.

4.2 Posologyandmethodofadministration

Therapyshouldbeinitiatedbyaphysicianexperiencedinthediagnosisandthetreatmentofpatients with CML.

Posology
Treatmentshouldbecontinuedaslongasclinicalbenefitisobservedoruntilunacceptabletoxicity occurs.

Ifadoseismissedthepatientshouldnottakeanadditionaldose,buttaketheusualprescribednext dose.

PosologyforPhiladelphiachromosomepositiveCMLadult patients
Therecommendeddoseis:
- 300mgtwicedailyinnewlydiagnosedpatientswithCMLinthechronic phase,
- 400mgtwicedailyinpatientswithchronicoracceleratedphaseCMLwithresistanceor intolerance to prior therapy.

PosologyforPhiladelphiachromosomepositiveCMLpaediatricpatients
Dosing in paediatric patients is individualised and is based on body surface area (mg/m^2). The recommended dose of nilotinib is 230 mg/m^2 twice daily, rounded to the nearest 50 mg dose (to a maximumsingledoseof400 mg)(seeTable1).DifferentstrengthsofTasignahardcapsulescanbe combined to attain the desired dose.

Thereisnoexperiencewithtreatment ofpaediatricpatientsbelow2 yearsofage.Therearenodatain newly diagnosed paediatric patients below 10 years of age and limited data in imatinib-resistant or intolerant paediatric patients below 6 years of age.

Table 1 Paediatricdosingschemeofnilotinib230mg/m^2twicedaily

BodySurfaceArea (BSA)	Dose in mg (twicedaily)
Upto0.32m^2	50 mg
0.33– 0.54m^2	100 mg
0.55– 0.76m^2	150 mg
0.77– 0.97m^2	200 mg
0.98– 1.19m^2	250 mg
1.20– 1.41m^2	300 mg
1.42– 1.63m^2	350 mg
≥1.64m^2	400 mg

*Adult Philadelphia chromosome positive CML patients in chronic phase who have been treated withnilotinib as first-line therapy and who achieved a sustained deep molecular response (MR4.5)*Discontinuation of treatment may be considered in eligible adult Philadelphia chromosome positive (Ph+)CML patients in chronic phase who have been treated with nilotinibat 300mg twicedailyfora minimumof3yearsifadeepmolecularresponse issustainedforaminimumofoneyearimmediately prior to discontinuation of therapy. Discontinuation of nilotinib therapy should be initiated by a physician experienced in the treatment of patients with CML (see sections 4.4 and 5.1).

Eligiblepatientswhodiscontinue nilotinibtherapymust havetheirBCR-ABLtranscriptlevelsand complete bloodcount withdifferentialmonitoredmonthly for one year,thenevery6 weeksforthe second year, and every 12 weeks thereafter. Monitoring of BCR-ABL transcript levels must be performedwithaquantitativediagnostictestvalidatedtomeasuremolecularresponselevelsonthe International Scale (IS) with a sensitivity of at least MR4.5 (BCR-ABL/ABL ≤0.0032% IS).

ForpatientswholoseMR4(MR4=BCR-ABL/ABL≤0.01%IS)butnotMMR (MMR=BCR-ABL/ABL≤0.1%IS)duringthetreatment-freephase,BCR-ABLtranscriptlevelsshould be monitored every 2 weeks until BCR-ABL levels return to a range between MR4 and MR4.5. PatientswhomaintainBCR-ABLlevelsbetweenMMRandMR4foraminimumof4 consecutive measurements can return to the original monitoring schedule.

PatientswholoseMMRmustre-initiatetreatmentwithin4 weeksofwhenlossofremissionisknown to have occurred. Nilotinib therapy should be re-initiated at 300 mg twice daily or at a reduced dose level of 400 mg once daily if the patient had a dose reduction prior to discontinuation of therapy. Patientswhore-initiatenilotinibtherapyshouldhavetheirBCR-ABLtranscriptlevelsmonitored monthly until MMR is re-established and every 12 weeks thereafter (see section 4.4).

*Adult Philadelphia chromosome positive CML patients in chronic phase who have achieved asustained deep molecular response (MR 4.5) on nilotinib following prior imatinib therapy*Discontinuation of treatment may be considered in eligible adult Philadelphia chromosome positive (Ph+)CMLpatientsinchronicphasewhohavebeentreatedwith nilotinibforaminimumof3yearsif a deep molecular response is sustained for a minimum of one year immediately prior to discontinuation of therapy. Discontinuation of nilotinib therapy should be initiated by a physician experienced in the treatment of patients with CML (see sections 4.4 and 5.1).

Eligible patients who discontinue nilotinibtherapymust have their BCR-ABL transcriptlevels and complete bloodcount with differentialmonitoredmonthly for one year,thenevery6 weeksforthe second year, and every 12 weeks thereafter. Monitoring of BCR-ABL transcript levels must be performedwithaquantitativediagnostictestvalidatedtomeasuremolecularresponselevels onthe International Scale (IS) with a sensitivity of at least MR4.5 (BCR-ABL/ABL ≤0.0032% IS).

Patients with confirmed loss of MR4 (MR4= BCR-ABL/ABL ≤0.01%IS) during the treatment-free phase(twoconsecutivemeasuresseparatedbyatleast4 weeksshowinglossofMR4) orlossofmajor molecular response (MMR=BCR-ABL/ABL ≤0.1%IS) must re-initiate treatment within 4 weeks of when loss of remission is known to have occurred. Nilotinib therapy should be re-initiated at either 300 mg or 400 mg twice daily. Patients who re-initiate nilotinib therapy should have their BCR-ABL transcript levels monitored monthly until previous major molecular response or MR4 level is re-establishedandevery12weeksthereafter(seesection4.4).

Doseadjustmentsormodifications
Tasignamayneedtobetemporarilywithheldand/ordosereducedforhaematologicaltoxicities (neutropenia,thrombocytopenia)thatarenotrelatedtotheunderlyingleukaemia(seeTable2).

Table 2 Doseadjustmentsforneutropeniaandthrombocytopenia

Adultpatientswithnewly diagnosed chronic phase CML at 300 mg twice daily and imatinib-resistant or intolerant CML in chronicphaseat400mg twicedaily	ANC*<1.0x10^9/land/or plateletcounts<50x 10^9/l	1. Treatment with nilotinib must be interruptedandbloodcountmonitored. 2. Treatmentmustberesumedwithin 2 weeks at prior dose if ANC >1.0x10^9/land/orplatelets>50x 10^9/l. 3. If blood counts remain low, a dose reductionto400mgoncedailymaybe required.
Adult patients with imatinib-resistantor intolerant CML in acceleratedphaseat 400 mg twice daily	ANC*<0.5x10^9/land/or plateletcounts<10x 10^9/l	1. Treatment with nilotinib must be interruptedandbloodcountmonitored. 2. Treatment must be resumed within2weeksatpriordoseifANC>1. 0x 10^9/l and/or platelets >20 x 10^9/l. 3. Ifbloodcountsremainlow,adose reductionto400mgoncedailymaybe required.
Paediatric patients with newlydiagnosedCMLin chronic phase at 230mg/m^2twicedaily and imatinib-resistantor intolerant CML in chronic phase at 230mg/m^2twicedaily	ANC*<1.0x10^9/land/or plateletcounts<50x 10^9/l	1. Treatment with nilotinib must be interruptedandbloodcountmonitored. 2. Treatmentmustberesumedwithin 2 weeks at prior dose if ANC >1.5x10^9/land/orplatelets>75x 10^9/l. 3. If blood counts remain low, a dose reductionto230mg/m^2oncedailymay be required. 4. Ifeventoccursafterdosereduction, consider discontinuing treatment.

*ANC=absoluteneutrophilcount

If clinically significant moderate or severe non-haematological toxicity develops, dosing should be interrupted, and patients should be monitored and treated accordingly. If the prior dose was 300 mg twicedailyinadultnewlydiagnosedpatientswithCMLinthechronicphase,or400mgtwicedailyin adult patients with imatinib-resistant or intolerant CML in chronic or acceleratedphase,or 230 mg/m^2 twicedailyin paediatric patients, dosing may beresumed at400 mg once daily inadult patients andat 230 mg/m^2 once daily in paediatric patients once the toxicity has resolved. If the prior dose was 400mgoncedailyinadultpatients or 230mg/m^2oncedaily inpaediatricpatients,treatment shouldbe discontinued. If clinically appropriate, re-escalation of the dose to the starting dose of 300 mg twice daily in adult newly diagnosed patients with CML in the chronic phase or to 400 mg twice daily in adult patients with imatinib-resistant or intolerant CML in chronic or accelerated phase or to 230mg/m^2twicedailyinpaediatricpatientsshouldbeconsidered.

Elevated serum lipase: For Grade 3-4 serum lipase elevations, doses in adult patients should be reducedto400mgoncedailyorinterrupted.Inpaediatricpatients,treatmentmustbe interrupteduntil the event returns to Grade ≤1. Thereafter, if the prior dose was 230 mg/m^2 twice daily, treatment can be resumed at 230mg/m^2 once daily. If the prior dosewas 230mg/m^2 once daily,treatment shouldbe discontinued.Serumlipaselevelsshouldbetestedmonthlyorasclinicallyindicated(seesection4.4).

Elevated bilirubin and hepatic transaminases: For Grade 3-4 bilirubin and hepatic transaminase elevations in adult patients, doses should be reduced to 400 mg once daily or interrupted. For Grade ≥2 bilirubin elevations or Grade ≥3 hepatic transaminase elevations in paediatric patients, treatmentmustbeinterrupteduntilthelevelsreturntoGrade≤1.Thereafter,ifthepriordosewas 230 mg/m^2 twice daily, treatment can be resumed at 230 mg/m^2 once daily. If the prior dose was 230 mg/m^2 once daily, and recovery to Grade ≤1 takes longer than 28 days, treatment should be discontinued.Bilirubinandhepatictransaminaseslevelsshouldbetestedmonthlyorasclinically indicated.

*Specialpopulations**Elde**rly*
Approximately12%ofsubjectsinthePhaseIIIstudyinpatientswithnewlydiagnosedCMLin chronic phase and approximately 30% of subjects in the Phase II study in patients with imatinib-resistantorintolerantCMLinchronicphaseandacceleratedphasewere65 yearsofageor over. No major differences were observed for safety and efficacy in patients ≥65 years of age as compared to adults aged 18 to 65 years.

Renal impairment
Clinicalstudieshavenotbeenperformedinpatientswithimpairedrenalfunction. Sincenilotinibanditsmetabolitesarenotrenallyexcreted,adecreaseintotalbodyclearanceisnot anticipated in patients with renal impairment.

Hepaticimpairment
Hepatic impairment has a modest effect on the pharmacokinetics of nilotinib. Dose adjustment is not consideredrecessaryinpatientswithhepaticimpairment.However,patientswithhepaticimpairment should be treated with caution (see section 4.4).

Cardiacdisorders
Inclinicalstudies,patientswithuncontrolledorsignificantcardiacdisease(e.g.,recentmyocardial infarction, congestive heart failure, unstable angina or clinically significant bradycardia) were excluded. Caution should be exercisedin patients withrelevant cardiacdisorders(see section 4.4).

Increasesintotalserumcholesterollevelshavebeenreportedwith nilotinibtherapy(seesection4.4). Lipid profiles should be determined prior to initiating nilotinib therapy, assessed at month 3 and 6 after initiating therapy and at least yearly during chronic therapy.

Increases in blood glucose levels have been reported with nilotinib therapy (see section 4.4). Blood glucoselevelsshouldbeassessedpriortoinitiatingnilotinibtherapyandmonitoredduringtreatment.

Paediatricpopulation
ThesafetyandefficacyofTasignainpaediatricpatientswithPhiladelphiachromosomepositive CML in chronic phase from 2 to less than 18 years of age have been established (see sections 4.8, 5.1 and 5.2). There is no experience in paediatric patients below 2 years of age or in paediatric patients with Philadelphia chromosome positive CML in accelerated phase or blast crisis. There are no data in newly diagnosed paediatric patients below 10 years of age and limited data in imatinib-resistant or intolerant paediatric patients below 6 years of age.

Methodofadministration

Tasigna should be taken twice daily approximately 12 hours apart and must not be taken with food. The hard capsules should be swallowed whole with water. No food should be consumed for 2 hours beforethedoseistakenandnofoodshouldbeconsumedforat leastonehourafterthedoseistaken.

For patients who are unable to swallow hard capsules, the content of each hard capsule may be dispersedinoneteaspoonofapplesauce(puréedapple)andshouldbetakenimmediately.Notmore than one teaspoon of apple sauce and no food other than apple sauce must be used (see sections 4.4 and 5.2).

4.3 Contraindications

Hypersensitivitytotheactivesubstanceortoanyoftheexcipients listedinsection6.1.

4.4 Specialwarningsandprecautionsforuse

Myelosuppression

Treatment with nilotinib is associated with (National Cancer Institute Common Toxicity Criteria grade 3 and 4) thrombocytopenia, neutropenia and anaemia. Occurrence is more frequent in patients with imatinib-resistant or intolerant CML, in particular in patients with accelerated-phase CML. Completebloodcountsshouldbeperformedeverytwoweeksforthefirst 2 monthsandthenmonthly thereafter,orasclinicallyindicated.Myelosuppressionwasgenerally reversibleandusuallymanaged by withholding Tasigna temporarily or dose reduction (see section 4.2).

QT prolongation

NilotinibhasbeenshowntoprolongcardiacventricularrepolarisationasmeasuredbytheQTinterval on the surface ECG in a concentration-dependent manner in adult and paediatric patients.

In the Phase III study in patients with newly diagnosed CML in chronic phase receiving 300 mg nilotinibtwicedaily,thechangefrombaselineinmeantime-averagedQTcFintervalatsteadystate was 6 msec. No patient had a QTcF >480 msec. No episodes of torsade de pointes were observed.

In the Phase II study in imatinib-resistant and intolerant CML patients in chronic and accelerated phasereceiving400mgnilotinibtwicedaily,thechangefrom baselineinmeantime-averagedQTcF interval at steady state was 5 and 8 msec, respectively.QTcF of >500 msec was observed in <1% of these patients. No episodes of torsade de pointes were observed in clinical studies.

Inahealthyvolunteerstudywithexposuresthatwerecomparabletotheexposuresobservedin patients, the time-averaged mean placebo-subtracted QTcF change from baseline was 7 msec (CI ± 4 msec). No subject had a QTcF >450 msec. Additionally, no clinically relevant arrhythmias wereobservedduringtheconductofthetrial.Inparticular,noepisodesoftorsadedepointes(transient or sustained) were observed.

SignificantprolongationoftheQTintervalmayoccurwhennilotinibisinappropriatelytakenwith strong CYP3A4 inhibitors and/or medicinal products with a known potential to prolong the QT interval, and/or food (see section 4.5). The presence of hypokalaemia and hypomagnesaemia may further enhancethis effect.Prolongationofthe QTintervalmay expose patientstotherisk offatal outcome.

TasignashouldbeusedwithcautioninpatientswhohaveorwhoareatsignificantriskofdevelopingprolongationofQTc,suchasthose:

- withcongenitallongQTprolongation
- withuncontrolledorsignificantcardiacdiseaseincludingrecent myocardialinfarction, congestive heart failure, unstable angina or clinically significant bradycardia.
- takinganti-arrhythmicmedicinalproductsorothersubstancesthatleadtoQTprolongation.

ClosemonitoringforaneffectontheQTcintervalisadvisableandabaselineECGisrecommended prior to initiating nilotinib therapy and as clinically indicated. Hypokalaemia or hypomagnesaemia must be corrected prior to Tasigna administration and should be monitored periodically during therapy.

Sudden death

Uncommon cases (0.1 to 1%) of sudden deaths have been reported in patients with imatinib-resistant orintolerantCMLinchronicphaseoracceleratedphase withapastmedicalhistoryofcardiacdisease or significant cardiac risk factors. Co-morbidities in addition to the underlying malignancy were also frequently present as were concomitant medicinal products. Ventricular repolarisation abnormalities may have been contributory factors. No cases of sudden death were reported in the Phase III study in newly diagnosed patients with CML in chronic phase.

Fluidretentionandoedema

Severe forms of drug-related fluid retention such as pleural effusion, pulmonary oedema, and pericardial effusion were uncommonly (0.1 to 1%) observed in a Phase III study of newly diagnosed CMLpatients.Similareventswereobservedinpost-marketingreports.Unexpected,rapidweightgain should be carefully investigated. If signs of severe fluid retention appear during treatment with nilotinib, the aetiology should be evaluated and patients treated accordingly (see section 4.2 for instructions on managing non-haematological toxicities).

Cardiovascularevents

Cardiovascular events were reported in a randomised Phase III study in newly diagnosed CMLpatients and observed in post-marketing reports. In this clinical study with a median on-therapy timeof 60.5 months, Grade 3-4 cardiovascular events included peripheral arterial occlusive disease (1.4% and1.1%at300mgand400mgnilotinibtwicedaily,respectively),ischaemicheartdisease(2.2%and 6.1% at 300 mg and 400 mg nilotinib twice daily, respectively) and ischaemic cerebrovascular events (1.1% and 2.2% at 300 mg and 400 mg nilotinib twice daily, respectively). Patients should be advised to seek immediate medical attention if they experience acute signs or symptoms of cardiovascular events. The cardiovascular status of patients should be evaluated and cardiovascular risk factors monitored and actively managed during nilotinib therapy according to standard guidelines. Appropriatetherapyshouldbeprescribedtomanagecardiovascularriskfactors(seesection 4.2for instructions on managing non-haematological toxicities).

HepatitisBreactivation

Reactivation of hepatitis B in patients who are chronic carriers of this virus has occurred after these patientsreceivedBCR-ABLtyrosinekinaseinhibitors.Somecases resultedinacutehepaticfailureor fulminant hepatitis leading to liver transplantation or a fatal outcome.

PatientsshouldbetestedforHBVinfectionbeforeinitiatingtreatment with nilotinib.Expertsinliver diseaseandinthetreatmentofhepatitisBshouldbeconsultedbeforetreatmentisinitiatedinpatients with positive hepatitis B serology (including those with active disease) and for patients who test positive for HBV infection during treatment. Carriers of HBV who require treatment with nilotinib shouldbecloselymonitoredforsignsandsymptomsofactiveHBVinfectionthroughouttherapyand for several months following termination of therapy (see section 4.8).

SpecialmonitoringofadultPh+CMLpatientsinchronicphasewhohaveachieved asustaineddeepmolecular response

Eligibilityfordiscontinuationoftreatment
Eligible patients who are confirmed to express the typical BCR-ABL transcripts, e13a2/b2a2 or e14a2/b3a2,canbeconsideredfortreatmentdiscontinuation.Patientsmust havetypicalBCR-ABL transcripts to allow quantitation of BCR-ABL, evaluation of the depth of molecular response, and determination of a possible loss of molecular remission after discontinuation of treatment with nilotinib.

Monitoringofpatientswhohavediscontinued therapy
Frequent monitoring of BCR-ABL transcript levels in patients eligible for treatment discontinuation must be performed with a quantitative diagnostic test validated to measure molecular response levels withasensitivityofatleastMR4.5(BCR-ABL/ABL≤0.0032%IS).BCR-ABLtranscriptlevelsmust be assessed prior to and during treatment discontinuation (see sections 4.2 and 5.1).

Lossofmajormolecularresponse(MMR=BCR-ABL/ABL≤0.1%IS)inCMLpatientswhoreceived nilotinib as first- or second-line therapy, or confirmed loss of MR4 (two consecutive measures separated by at least 4 weeks showing loss of MR4 (MR4=BCR-ABL/ABL ≤0.01%IS)) in CML patients who received nilotinib as second-line therapy will trigger treatment re-initiation within 4 weeks of when loss of remission is known to have occurred. Molecular relapse can occur during the treatment-free phase, and long-term outcome data are not yet available. It is therefore crucial to performfrequentmonitoringofBCR-ABLtranscriptlevelsandcompletebloodcountwithdifferential in order to detect possible loss of remission (see section 4.2). For patients who fail to achieve MMR after three months of treatment re-initiation, BCR-ABL kinase domain mutation testing should be performed.

Laboratorytestsandmonitoring

Bloodlipids
In a Phase III study in newly diagnosed CML patients, 1.1% of the patients treated with 400 mg nilotinib twice daily showed a Grade 3-4 elevation in total cholesterol; no Grade 3-4 elevations were however observed in the 300 mg twice daily dose group (see section 4.8). It is recommended that the lipid profiles be determined before initiating treatment with nilotinib, assessed at month 3 and 6 after initiatingtherapyandatleastyearlyduringchronictherapy(seesection4.2).IfaHMG-CoAreductase inhibitor (a lipid-lowering agent) is required, please refer to section 4.5 before initiating treatment since certain HMG-CoA reductase inhibitors are also metabolised by the CYP3A4 pathway.

Blood glucose
In a Phase III study in newly diagnosed CML patients, 6.9% and 7.2% of the patients treated with 400 mg nilotinib and 300 mg nilotinib twice daily, respectively, showed a Grade 3-4 elevation in bloodglucose.Itisrecommendedthattheglucoselevelsbeassessedbeforeinitiatingtreatmentwith Tasignaandmonitoredduringtreatment,asclinicallyindicated(seesection 4.2).Iftestresultswarrant therapy, physicians should follow their local standards of practice and treatment guidelines.

Interactionswithothermedicinalproducts

The administration of Tasigna with agents that are strong CYP3A4 inhibitors (including, but not limited to, ketoconazole, itraconazole, voriconazole, clarithromycin, telithromycin, ritonavir) shouldbe avoided. Should treatment with any of these agents be required, it is recommended that nilotinib therapybeinterruptedifpossible(seesection 4.5).Iftransientinterruptionoftreatmentisnotpossible, close monitoring of the individual for prolongation of the QT interval is indicated (see sections4.2,4.5 and 5.2).

Concomitant use of nilotinib with medicinal products that are potent inducers of CYP3A4 (e.g., phenytoin,rifampicin,carbamazepine,phenobarbitalandSt.John'sWort)islikely toreduceexposure to nilotinib to a clinically relevant extent. Therefore, in patients receiving nilotinib, co-administration of alternative therapeutic agents with less potential for CYP3A4 induction should be selected (see section 4.5).

Food effect

The bioavailability of nilotinib is increased by food. Tasigna must not be taken in conjunction with food(see sections 4.2 and 4.5) and should be taken 2 hours after a meal. No food should be consumed for at least one hour after the dose is taken. Grapefruit juice and other foods that are known to inhibit CYP3A4shouldbeavoided.Forpatientswhoareunabletoswallowhardcapsules,thecontentofeach hard capsule may be dispersed in one teaspoon of apple sauce and should be taken immediately. Not more than one teaspoon of apple sauce and no food other than apple sauce must be used (see section5.2).

Hepaticimpairment

Hepatic impairment has a modest effect on the pharmacokinetics of nilotinib. Single dose administration of 200 mg of nilotinib resulted in increases in AUC of 35%, 35% and 19% in subjects with mild, moderate and severe hepatic impairment, respectively, compared to a control group of subjects with normal hepatic function. The predicted steady-state C_{max} of nilotinib showed an increase of 29%, 18% and 22%, respectively. Clinical studies have excluded patients with alanine transaminase (ALT) and/or aspartate transaminase (AST) >2.5 (or >5, if related to disease) times the upper limit of the normal range and/or total bilirubin >1.5 times the upper limit of the normal range. Metabolism of nilotinib is mainly hepatic. Patients with hepatic impairment might therefore have increased exposure to nilotinib and should be treated with caution (see section 4.2).

Serum lipase

Elevation in serum lipase has been observed. Caution is recommended in patients with previous history of pancreatitis. In case lipase elevations are accompanied by abdominal symptoms, nilotinib therapy should be interrupted and appropriate diagnostic measures considered to exclude pancreatitis.

Totalgastrectomy

The bioavailability of nilotinib might be reduced in patients with totalgastrectomy (see section 5.2). More frequent follow-up of these patients should be considered.

Tumourlysis syndrome

Due to possible occurrence of tumourlysis syndrome (TLS) correction of clinically significant dehydration and treatment of high uric acid levels are recommended prior to initiating nilotinib therapy (see section 4.8).

Lactose

Tasigna hard capsules contain lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

Paediatricpopulation

Laboratory abnormalities of mild to moderate transient elevations of aminotransferases and total bilirubin have been observed in children at a higher frequency than in adults, indicating a higher risk of hepatotoxicity in the paediatric population (see section 4.8). Liver function (bilirubin and hepatic transaminases levels) should be monitored monthly or as clinically indicated. Elevations of bilirubin and hepatic transaminases should be managed by withholding nilotinib temporarily, dose reduction and/or discontinuation of nilotinib (see section 4.2). In a study in the CML paediatric population, growth retardation has been documented in patients treated with nilotinib (see section 4.8). Close monitoring of growth in paediatric patients under nilotinib treatment is recommended.

4.5 Interaction with other medicinal products and other forms of interaction

Tasigna may be given in combination with haematopoietic growth factors such as erythropoietin or granulocyte colony-stimulating factor (G-CSF) if clinically indicated. It may be given with hydroxyurea or anagrelide if clinically indicated.

Nilotinib is mainly metabolised in the liver with CYP3A4 expected to be the main contributor to the oxidative metabolism. Nilotinib is also a substrate for the multi-drug efflux pump, P-glycoprotein (P-gp). Therefore, absorption and subsequent elimination of systemically absorbed nilotinib may be influenced by substances that affect CYP3A4 and/or P-gp.

Substancesthatmayincreasenilotinibserumconcentrations

Concomitant administration of nilotinib with imatinib (a substrate and moderator of P-gp and CYP3A4),hadaslightinhibitoryeffectonCYP3A4and/orP-gp.TheAUCofimatinibwasincreased by 18% to 39%, and the AUC of nilotinib was increased by 18% to 40%. These changes are unlikely to be clinically important.

The exposure to nilotinib in healthy subjects was increased 3-fold when co-administered with the strong CYP3A4 inhibitor ketoconazole. Concomitant treatment with strong CYP3A4 inhibitors, including ketoconazole, itraconazole, voriconazole, ritonavir, clarithromycin, and telithromycin, shouldthereforebeavoided(seesection4.4).Increasedexposuretonilotinibmightalsobeexpected with moderate CYP3A4 inhibitors. Alternative concomitant medicinal products with no or minimal CYP3A4 inhibition should be considered.

Substancesthatmaydecreasenilotinibserum concentrations

Rifampicin,apotentCYP3A4inducer,decreasesnilotinibC_{max}by64%andreducesnilotinibAUCby 80%. Rifampicin and nilotinib should not be used concomitantly.

The concomitant administration of other medicinal products that induce CYP3A4 (e.g. phenytoin, carbamazepine,phenobarbitalandSt.John'sWort)islikewiselikelytoreduceexposuretonilotinibto a clinically relevant extent. In patients for whom CYP3A4 inducers are indicated, alternative agents with less enzyme induction potential should be selected.

NilotinibhaspHdependentsolubility,withlowersolubilityathigherpH.Inhealthysubjectsreceiving esomeprazole at 40 mg once daily for 5 days, gastric pH was markedly increased, but nilotinib absorption was only decreased modestly (27% decrease in $C_{max}$and 34% decrease in AUC_0-∞). Nilotinibmaybeusedconcurrentlywithesomeprazoleorotherprotonpumpinhibitorsasneeded.

Inastudyinhealthysubjects,nosignificantchangeinnilotinibpharmacokineticswasobservedwhen a single 400 mg dose of nilotinib was administered 10 hours after and 2 hours before famotidine. Therefore,whentheconcurrentuseofaH2blockerisnecessary,itmay beadministered approximately 10 hours before and approximately 2 hours after the dose of Tasigna.

In the same study as above, administration of an antacid (aluminium hydroxide/magnesium hydroxide/simethicone) 2 hours before or after a single 400 mg dose of nilotinib also did not alter nilotinibpharmacokinetics.Therefore,ifnecessary,anantacidmaybeadministeredapproximately 2 hours before or approximately 2 hours after the dose of Tasigna.

Substancesthatmayhavetheirsystemicconcentrationalteredby nilotinib

Invitro,nilotinibisarelativelystronginhibitorofCYP3A4,CYP2C8,CYP2C9,CYP2D6and UGT1A1, with Ki value being lowest for CYP2C9 (Ki=0.13 microM).

A single-dose drug-drug interaction study in healthy volunteers with 25 mg warfarin, a sensitive CYP2C9 substrate, and 800 mg nilotinib did not result in any changes in warfarin pharmacokinetic parameters or warfarin pharmacodynamics measured as prothrombin time (PT) and international normalisedratio(INR).Theareno steady-statedata.Thisstudysuggeststhataclinicallymeaningful drug-drug interaction between nilotinib and warfarin is less likely up to a dose of 25 mg of warfarin. Duetolackofsteady-statedata,controlofwarfarinpharmacodynamicmarkers(INRorPT)following initiation of nilotinib therapy (at least during the first 2 weeks) is recommended.

In CML patients, nilotinib administered at 400 mg twice daily for 12 days increased the systemic exposure (AUC and C_{max}) of oral midazolam (a substrate of CYP3A4) 2.6-fold and 2.0-fold, respectively. Nilotinib is a moderate CYP3A4 inhibitor. As a result, the systemic exposure of other medicinal products primarily metabolised by CYP3A4 (e.g. certain HMG-CoA reductase inhibitors) may be increased when co-administered with nilotinib. Appropriate monitoring and dose adjustment may be necessary for medicinal products that are CYP3A4 substrates and have a narrow therapeutic index(includingbutnotlimitedtoalfentanil,cyclosporine,dihydroergotamine,ergotamine,fentanyl, sirolimus and tacrolimus) when co-administered with nilotinib.

ThecombinationofnilotinibwiththosestatinsthataremainlyeliminatedbyCYP3A4,mayincrease the potential for statin-induced myopathy, including rhabdomyolysis.

Anti-arrhythmicmedicinalproductsandothersubstancesthatmayprolongtheQTinterval

Nilotinib should be used with cautionin patients who have or may develop prolongation of the QT interval, including those patients taking anti-arrhythmic medicinal products such as amiodarone, disopyramide,procainamide,quinidineandsotalolorothermedicinalproductsthatmayleadtoQT prolongation such as chloroquine, halofantrine, clarithromycin, haloperidol, methadone and moxifloxacin (see section 4.4).

Food interactions

The absorption and bioavailability of nilotinib are increased if it is taken with food, resulting in a higherserumconcentration(seesections 4.2,4.4and5.2).Grapefruitjuiceand otherfoodsthatare known to inhibit CYP3A4 should be avoided.

Paediatricpopulation

Interactionstudieshaveonlybeenperformedinadults.

4.6 Fertility,pregnancyandlactation

Womenofchildbearingpotential/Contraception

Womenofchildbearingpotentialhavetousehighlyeffectivecontraceptionduringtreatmentwith nilotinib and for up to two weeks after ending treatment.

Pregnancy

There are no or limited amount of data from the use of nilotinib in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). Tasigna should not be used during pregnancyunlesstheclinicalconditionofthewomanrequirestreatmentwithnilotinib.Ifitisused during pregnancy, the patient must be informed of the potential risk to the foetus.

If a woman who is being treated with nilotinib is considering pregnancy, treatment discontinuation may be considered based on the eligibility criteria for discontinuing treatment as described in sections 4.2 and 4.4. There is a limited amount of data on pregnancies in patients while attempting treatment-free remission (TFR). If pregnancy is planned during the TFR phase, the patient must be informedofapotentialneedtore-initiatenilotinibtreatmentduringpregnancy(seesections 4.2and 4.4).

Breast-feeding

It is unknown whether nilotinib is excreted in human milk. Available toxicological data in animals haveshownexcretionofnilotinibinmilk(seesection5.3).Sincearisktothenewborns/infantscannot be excluded, women should not breast-feed during Tasigna treatment and for 2 weeks after the last dose.

Fertility

Animalstudiesdidnotshowaneffectonfertilityinmaleandfemalerats(seesection5.3).

4.7 Effectsonabilitytodriveandusemachines

Tasigna has no or negligible influence on the ability to drive and use machines. However, it is recommended that patients experiencing dizziness, fatigue, visual impairment or other undesirable effectswithapotentialimpactontheabilitytodriveorusemachinessafelyshouldrefrainfromthese activities as long as the undesirable effects persist (see section 4.8).

4.8 Undesirableeffects

Summaryofthesafety profile

The safety profile is based on pooled data from 3,422 patients treated with Tasigna in 13 clinical studiesintheapprovedindications: adults and paediatric patients with newly diagnosed Philadelphia chromosomepositivechronicmyelogenousleukaemia(CML)inthechronicphase (5clinicalstudies with 2,414 patients), adult patients with chronic phase and accelerated phase Philadelphia chromosome positive CML with resistance or intolerance to prior therapy including imatinib (6 clinical studies with939 patients) and paediatric patients withchronic phase Philadelphia chromosomepositiveCMLwithresistanceorintolerancetopriortherapyincludingimatinib (2clinicalstudieswith69patients).Thesepooleddatarepresents9,039.34patient-yearsofexposure. The

safety profile of nilotinib is consistent across indications.

The most common adverse reactions (incidence ≥15%) from the pooled safety data were: rash (26.4%),upperrespiratorytractinfection(includingpharyngitis,nasopharyngitis,rhinitis)(24.8%) headache (21.9%), hyperbilirubinaemia (including blood bilirubin increased) (18.6%), arthralgia (15.8%), fatigue (15.4%), nausea (16.8%), pruritus (16.7%) and thrombocytopenia (16.4%).

Tabulatedlistofadversereactions

Adverse reactions from clinical studies and post-marketing reports (Table 3) are listed by MedDRA system organ class and frequency category. Frequency categories are defined using the following convention:verycommon(≥1/10);common(≥1/100to<1/10);uncommon(≥1/1,000to<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 3 Adversedrug reactions

Infectionsandinfestations	
Verycommon:	Upperrespiratorytractinfection(includingpharyngitis,nasopharyngitis, rhinitis)
Common:	Folliculitis,bronchitis,candidiasis(includingoralcandidiasis), pneumonia, gastroenteritis, urinary tract infection
Uncommon:	Herpesvirusinfection,analabscess,candidiasis(candidainfection), furuncle, sepsis, subcutaneous abscess, tinea pedis
Rare:	HepatitisBreactivation
Neoplasmsbenign,malignantandunspecified(includingcystsandpolyps)	
Uncommon:	Skin papilloma
Rare:	Oralpapilloma,paraproteinaemia
Bloodandlymphaticsystem disorders	
Verycommon:	Anaemia,thrombocytopenia
Common:	Leukopenia,leukocytosis,neutropenia,thrombocythaemia
Uncommon:	Eosinophilia,febrileneutropenia,lymphopenia,pancytopenia
Immunesystem disorders	
Uncommon:	Hypersensitivity
Endocrinedisorders	
Verycommon:	Growthretardation
Common:	Hypothyroidism
Uncommon:	Hyperthyroidism
Rare:	Hyperparathyroidismsecondary,thyroiditis
Metabolismandnutritiondisorders	
Common:	Electrolyte imbalance (including hypomagnesaemia, hyperkalaemia, hypokalaemia, hyponatraemia, hypocalcaemia, hypercalcaemia, hyperphosphataemia), diabetes mellitus, hyperglycaemia, hypercholesterolaemia, hyperlipidaemia, hypertriglyceridaemia, decreasedappetite,gout,hyperuricaemia,hypophosphataemia(including blood phosphorus decreased)
Uncommon:	Dehydration,increasedappetite,dyslipidaemia,hypoglycaemia
Rare:	Appetitedisorder,tumourlysissyndrome
Psychiatricdisorders	
Common:	Depression,insomnia,anxiety
Uncommon:	Amnesia,confusionalstate,disorientation
Rare:	Dysphoria
Nervoussystem disorders	
Verycommon:	Headache
Common:	Dizziness,hypoaesthesia,paraesthesia,migraine
Uncommon:	Cerebrovascularaccident,intracranial/cerebralhaemorrhage,ischaemic stroke, transient ischaemic attack, cerebral infarction, loss of consciousness (including syncope), tremor, disturbance in attention, hyperaesthesia, dysaesthesia, lethargy, peripheral neuropathy, restless legssyndrome,facialparalysis
Rare:	Basilararterystenosis,brainoedema,opticneuritis
Eyedisorders	
Common:	Conjunctivitis,dryeye(includingxerophthalmia),eyeirritation, hyperaemia (scleral, conjunctival, ocular), vision blurred
Uncommon:	Visual impairment, conjunctival haemorrhage, visual acuity reduced, eyelidoedema,blepharitis,photopsia,conjunctivitisallergic,diplopia, eye haemorrhage, eye pain, eye pruritus, eye swelling, ocular surface disease,periorbitaloedema,photophobia
Rare:	Chorioretinopathy,papilloedema

Earandlabyrinth disorders	
Common:	Vertigo,earpain, tinnitus
Uncommon:	Hearingimpaired(hypoacusis)
Cardiac disorders	
Common:	Angina pectoris, arrhythmia (including atroventricular block, cardiac flutter, ventricular extrasystoles, tachycardia, atrial fibrillation, bradycardia),palpitations,electrocardiogramQTprolonged,coronary arterydisease
Uncommon:	Myocardialinfarction,cardiacmurmur,pericardialeffusion,cardiac failure, diastolic dysfunction, left bundle branch block, pericarditis
Rare:	Cyanosis,ejectionfractiondecreased
Notknown:	Ventriculardysfunction
Vasculardisorders	
Common:	Hypertension,flushing,peripheralarterialocclusivedisease
Uncommon:	Hypertensivecrisis,intermittentclaudication,peripheralarterystenosis, haematoma, arteriosclerosis, hypotension, thrombosis
Rare:	Shock haemorrhagic
Respiratory,thoracicandmediastinaldisorders	
Verycommon:	Cough
Common:	Dyspnoea,dyspnoeaexertional,epistaxis,oropharyngealpain
Uncommon:	Pulmonaryoedema,pleuraleffusion,interstitiallungdisease,pleuritic pain,pleurisy,throatirritation,dysphonia,pulmonaryhypertension, wheezing
Rare:	Pharyngolaryngealpain
Gastrointestinaldisorders	
Verycommon:	Nausea,upperabdominalpain,constipation,diarrhoea,vomiting
Common:	Pancreatitis,abdominaldiscomfort,abdominaldistension,flatulence, abdominalpain,dyspepsia,gastritis,gastroesophagealreflux, haemorrhoids, stomatitis
Uncommon:	Gastrointestinalhaemorrhage,melaena,mouthulceration,oesophageal pain, dry mouth, sensitivity of teeth (hyperaesthesia teeth), dysgeusia, enterocolitis,gastriculcer,gingivitis,hiatushernia,rectalhaemorrhage
Rare:	Gastrointestinalulcerperforation,haematemesis,oesophagealulcer, oesophagitis ulcerative, retroperitoneal haemorrhage, subileus
Hepatobiliarydisorders	
Verycommon:	Hyperbilirubinaemia(includingbloodbilirubinincreased)
Common:	Hepaticfunctionabnormal
Uncommon:	Hepatotoxicity,toxichepatitis,jaundice,cholestasis,hepatomegaly
Skinandsubcutaneoustissue disorders	
Verycommon:	Rash,pruritus,alopecia
Common:	Night sweats, eczema, urticaria, hyperhidrosis, contusion, acne, dermatitis(includingallergic,exfoliativeandacneiform),dryskin, erythema
Uncommon:	Exfoliativerash,drugeruption,skinpain,ecchymosis,swellingface, blister, dermal cysts, erythema nodosum, hyperkeratosis, petechiae, photosensitivity,psoriasis, skin discolouration, skinexfoliation,skin hyperpigmentation,skinhypertrophy,skinulcer
Rare:	Erythemamultiforme,palmar-plantarerythrodysaesthesiasyndrome, sebaceous hyperplasia, skin atrophy
Musculoskeletalandconnectivetissuedisorders	
Verycommon	Myalgia,arthralgia,backpain,paininextremity
Common:	Musculoskeletalchestpain,musculoskeletalpain,neckpain,muscular weakness, muscle spasms, bone pain
Uncommon:	Musculoskeletalstiffness,jointswelling,arthritis,flankpain

Renalandurinary disorders	
Common:	Pollakiuria,dysuria
Uncommon:	Micturitionurgency,nocturia,chromaturia,haematuria,renalfailure, urinary incontinence
Reproductivesystemandbreast disorders	
Common:	Erectiledysfunction,menorrhagia
Uncommon:	Breastpain,gynaecomastia,nippleswelling
Rare:	Breast induration
Generaldisordersandadministrationsiteconditions	
Verycommon	Fatigue, pyrexia
Common:	Chestpain(includingnon-cardiacchestpain),pain,chestdiscomfort, malaise,astheniaandoedemaperipheral,chills,influenza-likeillness
Uncommon:	Faceoedema,gravitationaloedema,feelingbodytemperaturechange (includingfeelinghot,feelingcold),localisedoedema
Rare:	Sudden death
Investigations	
Verycommon:	Alanineaminotransferaseincreased,lipaseincreased
Common:	Haemoglobin decreased, blood amylase increased, aspartate aminotransferase increased, blood alkaline phosphatase increased, gamma-glutamyltransferase increased, blood creatinine phosphokinase increased,weightdecreased,weightincreased,elevatedcreatinine,total cholesterolincreased
Uncommon:	Blood lactate dehydrogenase increased, blood urea increased, blood bilirubinunconjugatedincreased,bloodparathyroidhormoneincreased, blood triglycerides increased, globulins decreased, lipoprotein cholesterol(includinglowdensityandhighdensity)increased,troponin increased
Rare:	Bloodglucosedecreased,bloodinsulindecreased,bloodinsulin increased, insulin C-peptide decreased

Note:Notalladversedrugreactionswereobservedinpaediatricstudies.

Description of selected adverse reactions

Sudden death
Uncommon cases (0.1 to 1%) of sudden deaths have been reported in Tasigna clinical studies and/or compassionateuseprogramsinpatientswithimatinib -resistantorintolerantCMLinchronicphaseor accelerated phase witha past medical history of cardiac disease orsignificant cardiacrisk factors(see section 4.4).

HepatitisB reactivation
HepatitisBreactivationhasbeenreportedinassociationwithBCR-ABLTKIs.Somecasesresultedin acute hepatic failure or fulminant hepatitis leading to liver transplantation or a fatal outcome (see section 4.4).

Paediatricpopulation

The safety of nilotinib in paediatric patients (from 2 to <18 years of age) with Philadelphia chromosome positive CML in chronic phase (n=58) has been investigated in one main study over a period of 60 months (see section 5.1). In paediatric patients, the frequency, type and severity of adverse reactions observed have been generally consistent with those observed in adults, with the exception of hyperbilirubinaemia/blood bilirubin increase (Grade 3/4: 10.3%) and transaminase elevation (AST Grade 3/4: 1.7%, ALT Grade 3/4: 12.1%) which were reported at a higher frequency thaninadultpatients.Bilirubinandhepatictransaminaselevelsshouldbemonitoredduringtreatment (see sections 4.2 and 4.4).

Growthretardationinpaediatricpopulation
In a study conducted in the CML paediatric population, with a median exposure of 51.9 months in newly diagnosed patients and 59.9 months in imatinib/dasatinib-resistant or imatinib-intolerant Ph+ CML-CPpatients,growthdeceleration(crossingatleasttwomainpercentilelinesfrombaseline)was observed in eight patients: five (8.6%) crossed two main percentile lines from baseline and three (5.2%) crossed three main percentile lines from baseline. Growth retardation related events were reported in 3 patients (5.2%). Close monitoring of growth in paediatric patients under nilotinib treatment is recommended (see section 4.4).

Reportingofsuspectedadversereactions

Reportingsuspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionalsareaskedtoreportanysuspectedadversereactions viathenationalreportingsystemlisted in Appendix V.

4.9 Overdose

Isolated reports of intentional overdose with nilotinib were reported, where an unspecified number of Tasignahardcapsuleswereingestedincombinationwithalcoholandothermedicinalproducts.Events included neutropenia, vomiting and drowsiness. No ECG changes or hepatotoxicity were reported. Outcomeswerereportedasrecovered.

Intheeventofoverdose,thepatientshouldbeobservedandappropriatesupportivetreatment given.

5. PHARMACOLOGICALPROPERTIES

5.1 Pharmacodynamicproperties

Pharmacotherapeuticgroup:Antineoplasticagents,BCR-ABLtyrosinekinaseinhibitors,ATC code: L01EA03.

Mechanismof action

NilotinibisapotentinhibitoroftheABLtyrosinekinaseactivityoftheBCR-ABLoncoproteinbothin cell lines and in primary Philadelphia-chromosome positive leukaemia cells. The substance binds with high affinity to the ATP-binding site in such a manner that it is a potent inhibitor of wild-type BCR-ABL and maintains activity against 32/33imatinib-resistant mutantformsofBCR-ABL. As a consequence of this biochemical activity, nilotinib selectively inhibits the proliferation and induces apoptosisincelllinesandinprimaryPhiladelphia-chromosomepositiveleukaemiacellsfromCML patients. In murinemodelsof CML,as asingleagent nilotinibreducestumour burden andprolongs survival following oral administration.

Pharmacodynamiceffects

Nilotinibhaslittleornoeffectagainstthemajorityofotherproteinkinasesexamined,includingSrc, except forthePDGF,KIT andEphrinreceptorkinases,whichitinhibitsatconcentrationswithinthe rangeachieved followingoraladministration at therapeutic dosesrecommendedfor the treatment of CML (see Table 4).

Table4Kinaseprofileofnilotinib(phosphorylationIC_{50} nM)

BCR-ABL	PDGFR	KIT
20	69	210

Clinicalefficacy

Clinicalstudiesinnewlydiagnosed CML in chronic phase

Anopen-label,multicentre,randomisedPhase IIIstudywasconductedtodeterminetheefficacyof nilotinib versus imatinib in 846 adult patients with cytogenetically confirmed newly diagnosed Philadelphia chromosome positive CML in the chronic phase. Patients were within six months of diagnosis and were previously untreated, with the exception of hydroxyurea and/or anagrelide. Patientswererandomised1:1:1toreceiveeithernilotinib300mgtwicedaily(n=282),nilotinib 400mgtwicedaily(n=281)orimatinib400mgoncedaily(n=283).Randomisationwasstratifiedby Sokal risk score at the time of diagnosis.

Baselinecharacteristicswerewellbalancedbetweenthethreetreatmentarms.Medianagewas 47 years in both nilotinib arms and 46 years in the imatinib arm, with 12.8%, 10.0% and 12.4% of patients were ≥65 years of age in the nilotinib 300 mg twice daily, nilotinib 400 mg twice daily and imatinib 400 mg once daily treatment arms, respectively. There were slightly more male than female patients (56.0%, 62.3% and 55.8%, in the nilotinib 300 mg twice daily, 400 mg twice daily and imatinib400mgoncedailyarm,respectively).Morethan60%ofallpatientswereCaucasianand25% of all patients were Asian.

Theprimarydataanalysistimepointwaswhenall846patientscompleted12monthsoftreatment(or discontinued earlier). Subsequent analyses reflect when patients completed 24, 36, 48, 60 and 72 months of treatment (or discontinued earlier). The median time on treatment was approximately 70monthsinthenilotinibtreatmentgroupsand64monthsintheimatinibgroup.Themedianactual dose intensity was 593 mg/day for nilotinib 300 mg twice daily, 772 mg/day for nilotinib 400 mg twice daily and 400 mg/day for imatinib 400 mg once daily. This study is ongoing.

The primary efficacy endpoint was major molecular response (MMR) at 12 months. MMR was defined as ≤0.1% BCR-ABL/ABL% by international scale (IS) measured by RQ-PCR, which correspondstoa≥3logreductionofBCR-ABLtranscriptfromstandardisedbaseline.TheMMRrate at 12 months was statistically significantly higher for nilotinib 300 mg twice daily compared to imatinib 400 mg once daily (44.3% versus 22.3%, p<0.0001). The rate of MMR at 12 months, was also statistically significantly higher for nilotinib 400 mg twice daily compared to imatinib 400 mg once daily (42.7% versus 22.3%, p<0.0001).

TheratesofMMRat 3,6,9and12monthswere8.9%,33.0%,43.3%and44.3%fornilotinib300mg twicedaily,5.0%,29.5%,38.1%and42.7%fornilotinib400mgtwicedailyand0.7%,12.0%,18.0% and 22.3% for imatinib 400 mg once daily.

TheMMRrateat12,24,36,48,60and72monthsispresentedinTable5.

Table 5 MMRrate

	Nilotinib 300mgtwicedaily n=282 (%)	Nilotinib 400mgtwicedaily n=281 (%)	Imatinib 400mgoncedaily n=283 (%)
MMRat12months			
Response(95%CI)	44.3[1](38.4;50.3)	42.7[1](36.8;48.7)	22.3(17.6; 27.6)
MMRat24 months			
Response(95%CI)	61.7[1](55.8;67.4)	59.1[1](53.1;64.9)	37.5(31.8; 43.4)
MMRat36 months[2]			
Response(95%CI)	58.5[1](52.5;64.3)	57.3[1](51.3;63.2)	38.5(32.8; 44.5)
MMRat48 months[3]			
Response(95%CI)	59.9[1](54.0;65.7)	55.2(49.1; 61.1)	43.8(38.0; 49.8)
MMRat60 months[4]			
Response(95%CI)	62.8(56.8; 68.4)	61.2(55.2; 66.9)	49.1(43.2; 55.1)
MMRat72 months[5]			
Response(95%CI)	52.5(46.5; 58.4)	57.7(51.6; 63.5)	41.7(35.9; 47.7)

[1]Cochran-Mantel-Haenszel(CMH)testp-valueforresponserate(vs.imatinib400mg)<0.0001

[2]Only patients who were in MMR at a specific time point are included as responders for that time point. A total of 199 (35.2%) of all patients were not evaluable for MMR at 36 months (87 in the nilotinib300mgtwicedailygroupand112intheimatinibgroup)duetomissing/unevaluablePCR assessments (n=17), atypical transcripts at baseline (n=7), or discontinuation prior tothe36-month time point (n=175).

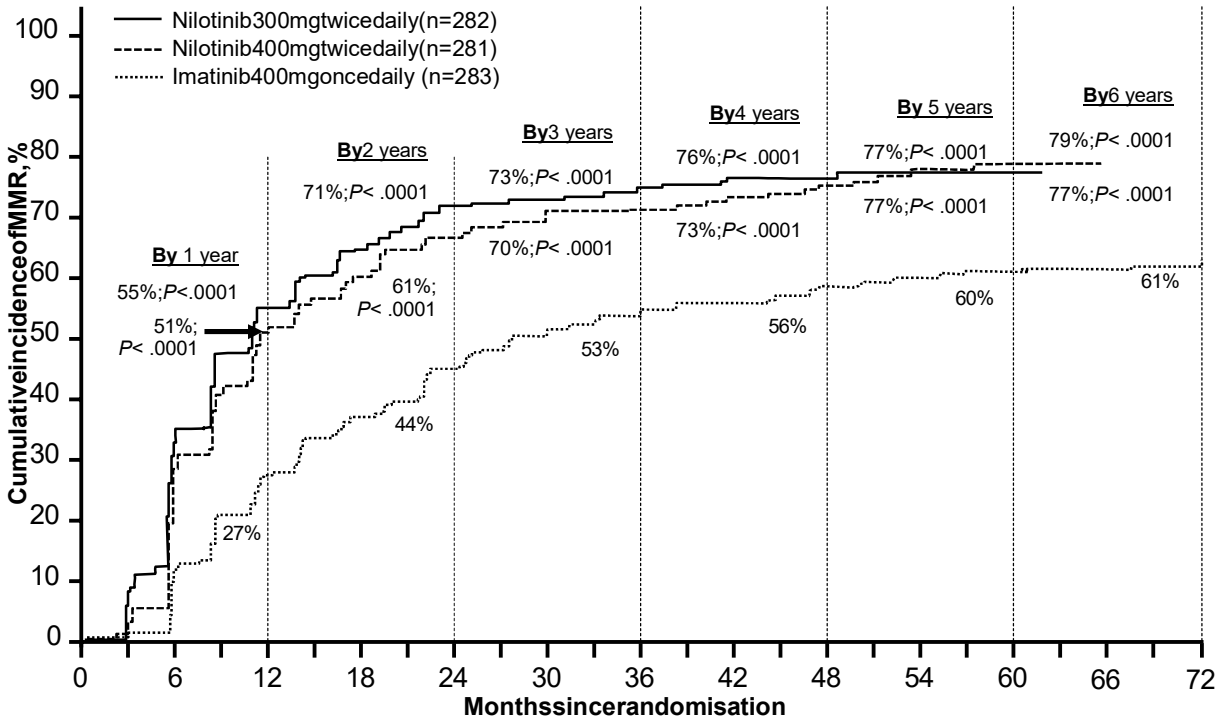
[3]Only patients who were in MMR at a specific time point are included as responders for that time point. A total of 305 (36.1%) of all patients were not evaluable for MMR at 48 months (98 in the nilotinib300mgBIDgroup,88inthenilotinib400mgBIDgroupand119intheimatinibgroup)due to missing/unevaluable PCR assessments (n=18), atypical transcripts at baseline (n=8), or discontinuation prior to the 48-month time point (n=279).

[4]Only patients who were in MMR at a specific time point are included as responders for that time point. A total of 322 (38.1%) of all patients were not evaluable for MMR at 60 months (99 in the nilotinib 300 mg twice daily group, 93 in the nilotinib 400 mg twice daily group and 130 in the imatinibgroup)duetomissing/unevaluablePCRassessments(n=9),atypicaltranscriptsatbaseline (n=8) or discontinuation prior to the 60-month time point (n=305).

[5]Only patients who were in MMR at a specific time point are included as responders for that time point. A total of 395 (46.7%) of all patients were not evaluable for MMR at 72 months (130 in the nilotinib 300 mg twice daily group, 110 in the nilotinib 400 mg twice daily group and 155 in the imatinibgroup)duetomissing/unevaluablePCRassessments(n=25),atypicaltranscriptsatbaseline (n=8) or discontinuation prior to the 72-month time point (n=362).

MMRratesbydifferenttimepoints(includingpatientswhoachievedMMRatorbeforethosetime points as responders) are presented in the cumulative incidence of MMR (see Figure 1).

Figure1 CumulativeincidenceofMMR



ForallSokalriskgroups,theMMRratesatalltimepointsremainedconsistentlyhigherinthetwo nilotinib groups than in the imatinib group.

Inaretrospectiveanalysis,91%(234/258)ofpatientsonnilotinib300mgtwicedaily achieved BCR-ABLlevels≤10%at3monthsoftreatmentcomparedto67%(176/264)ofpatientsonimatinib 400 mg once daily. Patients with BCR-ABL levels ≤10% at 3 months of treatment show a greater overall survival at 72 months compared to those who did not achieve this molecular response level (94.5% vs. 77.1% respectively [p=0.0005]).

Based on the Kaplan-Meier analysis of time to first MMR the probability of achieving MMR at differenttimepointswashigherforbothnilotinibat 300 mgand400mgtwicedailycomparedto imatinib400mgoncedaily(HR=2.17andstratifiedlog-rankp<0.0001betweennilotinib300 mg twice daily and imatinib 400 mg once daily, HR=1.88 and stratified log-rank p<0.0001 between nilotinib 400 mg twice daily and imatinib 400 mg once daily).

Theproportionofpatientswhohadamolecularresponseof≤0.01%and≤0.0032%byISatdifferent time points are presented in Table 6 and the proportion of patients who had a molecular response of ≤0.01% and ≤0.0032% by IS by different time points are presented in Figures 2 and 3. Molecular responsesof≤0.01%and≤0.0032%byIScorrespondtoa≥4 logreductionand≥4.5 logreduction, respectively, of BCR-ABL transcripts from a standardised baseline.

Table 6 Proportionsofpatientswhohadmolecularresponseof≤0.01%(4logreduction)and ≤0.0032%(4.5log reduction)

	Nilotinib 300mgtwicedaily n=282 (%)		Nilotinib 400mgtwicedaily n=281 (%)		Imatinib 400mgoncedaily n=283 (%)	
	≤0.01%	**≤0.0032%**	**≤0.01%**	**≤0.0032%**	**≤0.01%**	**≤0.0032%**
At12months	11.7	4.3	8.5	4.6	3.9	0.4
At24months	24.5	12.4	22.1	7.8	10.2	2.8
At36months	29.4	13.8	23.8	12.1	14.1	8.1
At48months	33.0	16.3	29.9	17.1	19.8	10.2
At60months	47.9	32.3	43.4	29.5	31.1	19.8
At72months	44.3	31.2	45.2	28.8	27.2	18.0

Figure2 Cumulativeincidenceofmolecularresponseof≤0.01%(4-logreduction)

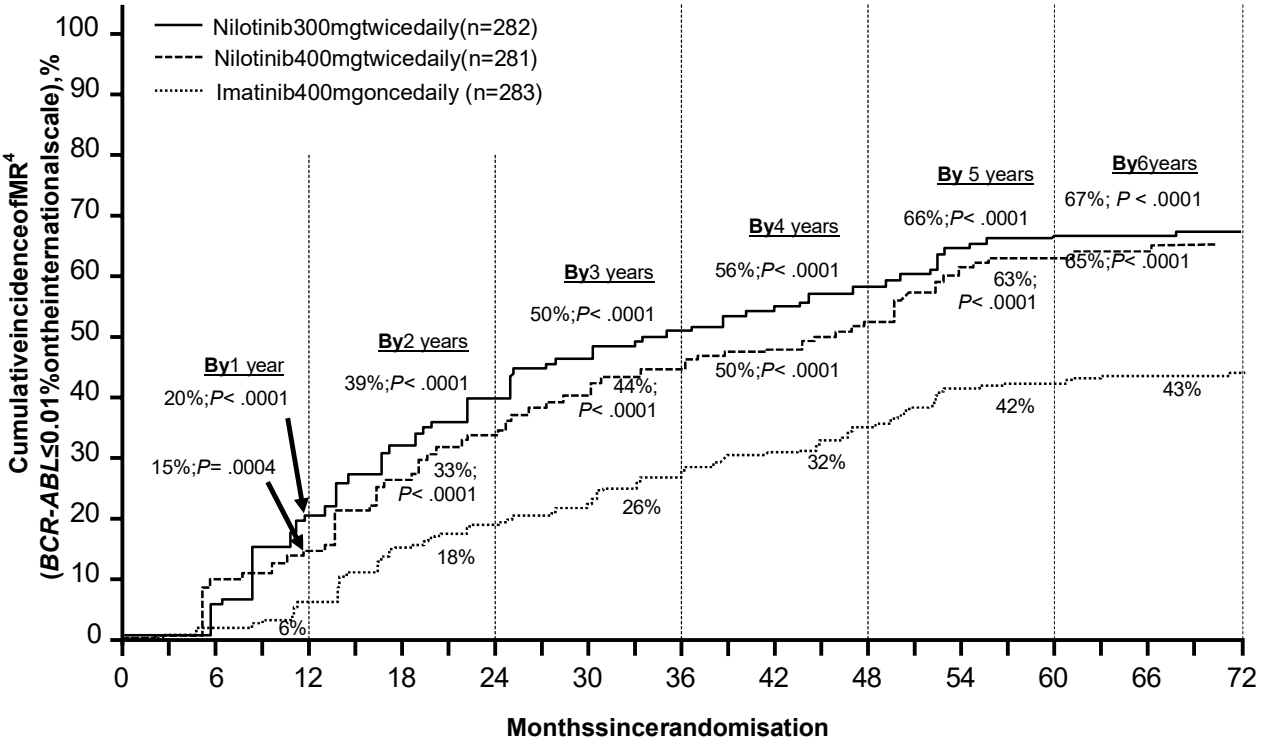
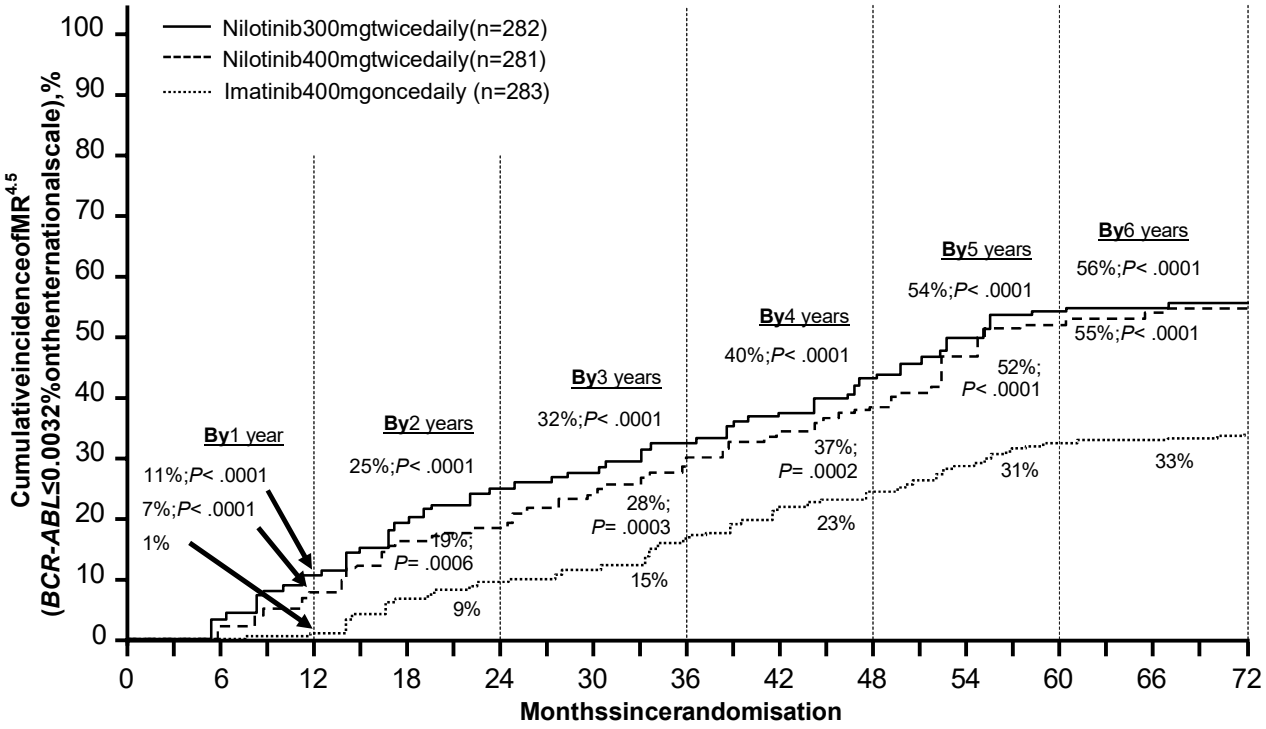


Figure3 Cumulativeincidenceofmolecularresponseof≤0.0032%(4.5logreduction)



BasedonKaplan-Meierestimates ofthedurationoffirstMMR,theproportionsofpatientswhowere maintaining response for 72 months among patients who achieved MMR were 92.5% (95% CI: 88.6-96.4%) in the nilotinib 300 mg twice daily group, 92.2% (95% CI: 88.5-95.9%) in the nilotinib 400mgtwicedailygroupand88.0%(95%CI:83.0-93.1%)intheimatinib400mgoncedailygroup.

Completecytogeneticresponse(CCyR)wasdefinedas0%Ph+metaphasesinthebonemarrowbased on a minimum of 20 metaphases evaluated. Best CCyR rate by 12 months (including patients who achieved CCyR at or before the 12 month time point as responders) was statistically higher for both nilotinib 300 mg and 400 mg twice daily compared to imatinib 400 mg once daily, see Table 7.

CCyRrateby24months(includespatientswhoachievedCCyRat orbeforethe24 monthtimepoint as responders) was statistically higher for both the nilotinib 300 mg twice daily and 400 mg twice daily groups compared to the imatinib 400 mg once daily group.

Table 7 BestCCyRrate

	Nilotinib 300mgtwice daily n=282 (%)	Nilotinib 400mgtwice daily n=281 (%)	Imatinib 400mgoncedaily n=283 (%)
By12 months			
Response(95%CI)	80.1(75.0; 84.6)	77.9(72.6; 82.6)	65.0(59.2; 70.6)
No response	19.9	22.1	35.0
CMHtestp-valueforresponserate (versusimatinib400mgonce daily)	<0.0001	0.0005	
By24 months			
Response(95%CI)	86.9(82.4; 90.6)	84.7(79.9; 88.7)	77.0(71.7; 81.8)
No response	13.1	15.3	23.0
CMHtestp-valueforresponserate (versus imatinib 400 mg once daily)	0.0018	0.0160	

Based on Kaplan-Meier estimates, the proportions of patients who were maintaining response for 72monthsamongpatientswhoachievedCCyRwere99.1%(95%CI:97.9-100%)inthenilotinib 300mgtwicedailygroup,98.7%(95%CI: 97.1-100%)inthenilotinib400mgtwicedailygroupand 97.0% (95% CI: 94.7-99.4%) in the imatinib 400 mg once daily group.

Progressiontoacceleratedphase(AP)orblastcrisis(BC)ontreatmentisdefinedasthetimefromthe date of randomisation to the first documented disease progression to accelerated phase or blast crisis or CML-related death. Progressionto accelerated phaseor blast crisis on treatmentwas observed ina total of 17 patients: 2 patients on nilotinib 300 mg twice daily, 3 patients on nilotinib 400 mg twice daily and 12 patients on imatinib 400 mg once daily. The estimated rates of patients free from progression to accelerated phase or blast crisis at 72 months were 99.3%, 98.7% and 95.2%, respectively (HR=0.1599 and stratified log-rank p=0.0059 between nilotinib 300 mg twice daily and imatinib once daily, HR=0.2457 and stratified log-rank p=0.0185 between nilotinib 400 mg twice daily and imatinib once daily). No new events of progression to AP/BC were reported on-treatment since the 2-year analysis.

Including clonal evolution as a criterion for progression, a total of 25 patients progressed to acceleratedphaseorblastcrisisontreatmentbythecut-offdate(3inthenilotinib300 mgtwicedaily group, 5 in the nilotinib 400 mg twice daily group and 17 in the imatinib 400 mg once daily group). The estimated rates of patients free from progression to accelerated phase or blast crisis including clonalevolutionat72monthswere98.7%,97.9%and93.2%,respectively(HR=0.1626andstratified log-rank p=0.0009 between nilotinib 300 mg twice daily and imatinib once daily, HR=0.2848 and stratified log-rank p=0.0085 between nilotinib 400 mg twice daily and imatinib once daily).

Atotalof55patientsdiedduringtreatmentorduringthefollow-upafterdiscontinuationoftreatment (21 in the nilotinib 300 mg twice daily group, 11 in the nilotinib 400 mg twice daily group and 23 in theimatinib400mgoncedailygroup).Twenty-six(26)ofthese55deathswererelatedtoCML(6in the nilotinib 300 mg twice daily group, 4 in the nilotinib 400 mg twice daily group and 16 in the imatinib 400 mg once daily group). The estimated rates of patients alive at 72 months were 91.6%, 95.8% and 91.4%, respectively (HR=0.8934 and stratified log-rank p=0.7085 between nilotinib 300mgtwicedailyandimatinib,HR=0.4632andstratifiedlog-rankp=0.0314betweennilotinib 400mgtwicedailyandimatinib).ConsideringonlyCML-relateddeathsasevents,theestimatedrates of overall survival at 72 months were 97.7%, 98.5% and 93.9%, respectively (HR=0.3694 and stratified log-rank p=0.0302 between nilotinib 300 mg twice daily and imatinib, HR=0.2433 and stratified log-rank p=0.0061 between nilotinib 400 mg twice daily and imatinib).

Clinicalstudiesinimatinib-resistantorintolerantCMLinchronicphaseandacceleratedphase
An open-label, uncontrolled, multicentre Phase II study was conducted to determine the efficacy of nilotinib in adult patients with imatinib resistant or intolerant CML with separate treatment arms for chronic and accelerated phase disease. Efficacy was based on 321 CP patients and 137 AP patients enrolled.Mediandurationoftreatmentwas561daysforCPpatientsand264daysforAPpatients(see Table 8). Tasigna was administered on a continuous basis (twice daily 2 hours after a meal and withno foodfor at least onehour after administration) unless there was evidence of inadequateresponseor disease progression. The dose was 400 mg twice daily and dose escalation to 600 mg twice daily was allowed.

Table 8 Durationofexposurewithnilotinib

	Chronicphase n=321	Acceleratedphase n=137
Mediandurationoftherapyindays (25th-75thpercentiles)	561 (196-852)	264 (115-595)

Resistance to imatinib included failure to achieve a complete haematological response (by 3 months), cytogenetic response (by 6 months) or major cytogenetic response (by 12 months) or progression of diseaseafterapreviouscytogeneticorhaematologicalresponse.Imatinibintoleranceincludedpatients who discontinued imatinib because of toxicity and were not in major cytogenetic response at time of study entry.

Overall,73%ofpatientswereimatinib-resistant,while27%wereimatinib-intolerant.Themajorityof patients had a long history of CML that included extensive prior treatment with other antineoplastic agents, including imatinib, hydroxyurea, interferon, and some had even failed organ transplant (Table9).Themedianhighestpriorimatinibdosehadbeen600 mg/day.Thehighestpriorimatinib dose was ≥600 mg/day in 74% of all patients, with 40% of patients receiving imatinib doses ≥800 mg/day.

Table 9 CMLdiseasehistorycharacteristics

	Chronicphase (n=321)	Acceleratedphase (n=137)*
Mediantimesincediagnosisinmonths (range)	58 (5–275)	71 (2–298)
Imatinib Resistant IntolerantwithoutMCyR	 226 (70%) 95 (30%)	 109 (80%) 27 (20%)
Mediantimeofimatinibtreatmentin days (25^{th}-75^{th}percentiles)	975 (519-1,488)	857 (424-1,497)
Prior hydroxyurea	83%	91%
Priorinterferon	58%	50%
Priorbonemarrowtransplant	7%	8%
*Missinginformationonimatinib-resistant/intolerantstatusforonepatient.		

The primary endpoint in the CP patients was major cytogenetic response (MCyR), defined as elimination(CCyR,completecytogeneticresponse)orsignificantreductionto<35%Ph+metaphases (partialcytogeneticresponse)ofPh+haematopoieticcells.Completehaematologicalresponse(CHR) in CP patients was evaluated as a secondary endpoint. The primary endpoint in the AP patients was overall confirmed haematological response (HR), defined as either a complete haematological response, no evidence of leukaemia or return to chronic phase.

Chronic phase
The MCyR rate in 321 CP patients was 51%. Most responders achieved their MCyR rapidly within 3 months (median 2.8 months) of starting nilotinib treatment and these were sustained. The median time to achieve CCyR was just past 3 months (median 3.4 months). Of the patients who achieved MCyR, 77% (95% CI: 70% - 84%) were maintaining response at 24 months. Median duration of MCyRhas not beenreached. Of the patients who achieved CCyR, 85% (95% CI:78% -93%) were maintainingresponseat24 months.Median duration of CCyR has not beenreached. Patients witha CHRatbaselineachievedaMCyRfaster(1.9versus2.8 months).OfCPpatientswithoutabaseline CHR, 70% achieved a CHR, median time to CHR was 1 month and median duration of CHR was 32.8months.Theestimated24-monthoverallsurvivalrateinCML-CPpatientswas87%.

Acceleratedphase
The overall confirmed HR rate in 137 AP patients was 50%. Most responders achieved a HR early with nilotinib treatment (median 1.0 months) and these have been durable (median duration of confirmedHRwas24.2months).OfthepatientswhoachievedHR,53%(95%CI:39% -67%)were maintaining response at 24 months. MCyR rate was 30% with a median time to response of 2.8 months. Of the patients who achieved MCyR, 63% (95% CI: 45% - 80%) were maintaining responseat24months.MediandurationofMCyRwas32.7months.Theestimated24-monthoverall survival rate in CML-AP patients was 70%.

TheratesofresponseforthetwotreatmentarmsarereportedinTable 10.

Table 10 ResponseinCML

(Bestresponserate)	**Chronicphase**			**Acceleratedphase**		
	Intolerant (n=95)	**Resistant (n=226)**	**Total (n=321)**	**Intolerant (n=27)**	**Resistant (n=109)**	**Total* (n=137)**
Haematological Response (%)						
Overall(95%CI) Complete NEL Returnto CP	- 87 (74-94) - -	- 65 (56-72) - -	- 70[1] (63-76) -	48 (29-68) 37 7 4	51 (42-61) 28 10 13	50 (42-59) 30 9 11
Cytogenetic Response(%)						
Major(95%CI) Complete Partial	57 (46-67) 41 16	49 (42-56) 35 14	51(46-57) 37 15	33 (17-54) 22 11	29 (21-39) 19 10	30 (22-38) 20 10

NEL=noevidenceofleukaemia/marrowresponse
[1]114CPpatientshadaCHRatbaselineandwerethereforenotassessableforcomplete haematological response
*Missinginformationonimatinib-resistant/intolerantstatusforonepatient.

Efficacy data in patients with CML-BC are not yet available. Separate treatment arms were also includedinthe Phase IIstudy toinvestigate Tasignaina group of CPand APpatients who had been extensivelypre-treatedwithmultipletherapiesincludingatyrosinekinaseinhibitoragentinaddition to imatinib. Of these patients 30/36 (83%) were treatment resistant not intolerant. In 22 CP patients evaluated for efficacy nilotinib induced a 32% MCyR rate and a 50% CHR rate. In 11 AP patients, evaluated for efficacy, treatment induced a 36% overall HR rate.

Afterimatinibfailure,24differentBCR-ABLmutationswerenotedin42%ofchronicphaseand54% of accelerated phase CML patients who were evaluated for mutations. Tasigna demonstrated efficacy in patients harboring a variety of BCR-ABL mutations associated with imatinib resistance, except T315I.

TreatmentdiscontinuationinadultPh+CMLpatientsinchronicphasewhohavebeentreatedwithnilotinib as first-line therapy and who have achieved a sustained deep molecular response

In an open-label, single-arm study, 215 adult patients with Ph+ CML in chronic phase treated with nilotinib in first-line for ≥2 years who achieved MR4.5 as measured with the MolecularMD MRDx BCR-ABL test were enrolled to continue nilotinib treatment for additional 52 weeks (nilotinib consolidationphase).190of215 patients(88.4%)enteredtheTFRphaseafterachievingasustained deep molecular response during the consolidation phase, defined by the following criteria:

- the4lastquarterlyassessments(takenevery12weeks)wereatleastMR4.0(BCR-ABL/ABL ≤0.01%IS),andmaintainedforoneyear
- thelastassessmentbeingMR4.5(BCR-ABL/ABL≤0.0032%IS)
- nomorethantwoassessmentsfallingbetweenMR4.0andMR4.5 (0.0032% IS < BCR-ABL/ABL ≤0.01% IS).

TheprimaryendpointwasthepercentageofpatientsinMMRat48 weeksafterstartingtheTFRphase (considering any patient who required re-initiation of treatment as non-responder).

Table 11 Treatment-freeremissionafternilotinibfirst-linetreatment

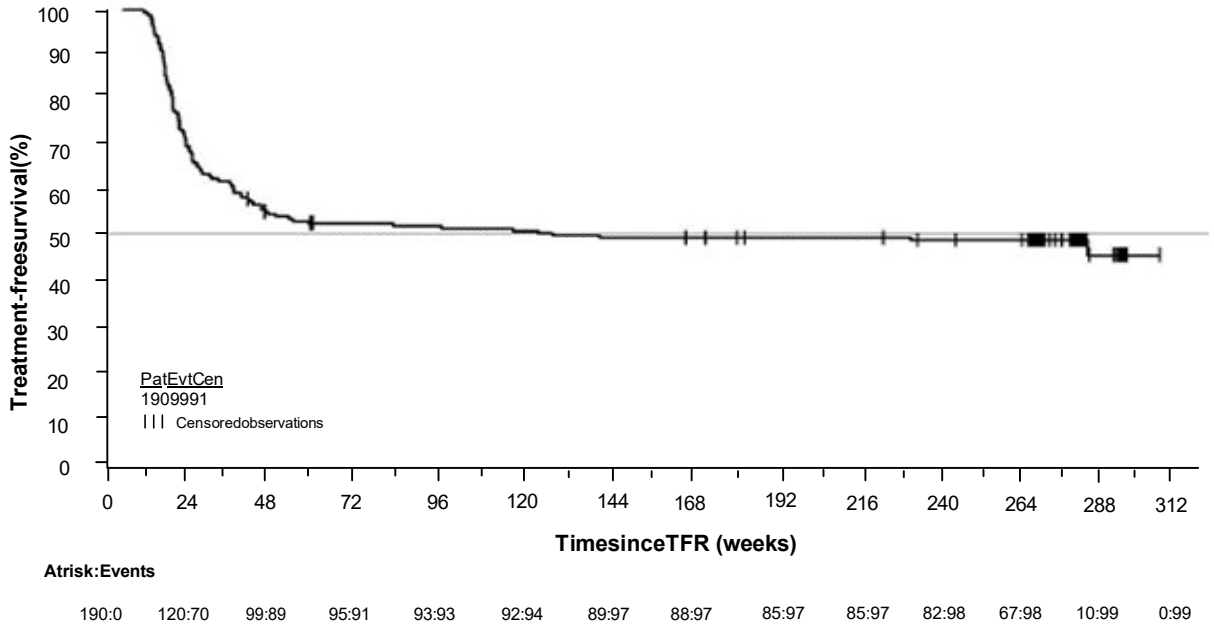
PatientsenteredTFRphase	190	
weeksafterstartingTFRphase	48 weeks	264 weeks
patientsremaininginMMRor better	98(51.6%,[95%CI:44.2, 58.9])	79[2](41.6%,95%CI: 34.5, 48.9)
PatientsdiscontinuedTFRphase	93 [1]	109
duetoloss ofMMR	88 (46.3%)	94 (49.5%)
duetoother reasons	5	15
Patientsrestartedtreatmentafterlossof MMR	86	91
regainingMMR	85 (98.8%)	90 (98.9%)
regaining MR4.5	76 (88.4%)	84 (92,3%)

[1] OnepatientdidnotloseMMRbyweek48butdiscontinuedTFR phase.
[2] For2patients,PCRassessmentwasnotavailableat week264thereforetheirresponsewasnot considered for the week 264 data cut-off analysis.

Thetimebywhich50%ofallretreatedpatientsregainedMMRandMR4.5was7and12.9 weeks, respectively. The cumulative rate of MMR regained at 24 weeks aftertreatment re-initiation was 97.8% (89/91 patients) and MR4.5 regained at 48 weeks was 91.2% (83/91 patients).

TheKaplan-Meierestimateofmediantreatment-freesurvival(TFS) was120.1weeks(95%CI:36.9, not estimable [NE]) (Figure 4); 91 of 190 patients (47.9%) did not have a TFS event.

Figure 4 Kaplan-Meierestimateoftreatment-freesurvivalafterstartofTFR(fullanalysis set)



TreatmentdiscontinuationinadultCMLpatientsinchronicphasewhohaveachievedasustaineddeep molecular response on nilotinib treatment following prior imatinib therapy

In an open-label, single-arm study, 163 adult patientswith Ph+ CML in chronic phase taking tyrosine kinase inhibitors (TKIs) for ≥3 years (imatinib as initial TKI therapy for more than 4 weeks without documentedMR4.5onimatinibatthetimeofswitchtonilotinib,thenswitchedtonilotinibforatleast two years), and who achieved MR4.5 on nilotinib treatment as measured with the MolecularMD MRDx BCR-ABL test were enrolledto continue nilotinib treatment for additional 52 weeks(nilotinib consolidation phase). 126 of 163 patients (77.3%) entered the TFR phase after achieving a sustained deep molecular response during the consolidation phase, defined by the following criterion:

- The4lastquarterlyassessments(takenevery12 weeks)showednoconfirmedlossofMR4.5 (BCR-ABL/ABL ≤0.0032% IS) during one year.

Theprimaryendpointwastheproportionofpatientswithoutconfirmedlossof MR4.0orlossofMMR within 48 weeks following treatment discontinuation.

Table 12 Treatment-freeremissionafternilotinibtreatmentfollowingpriorimatinibtherapy

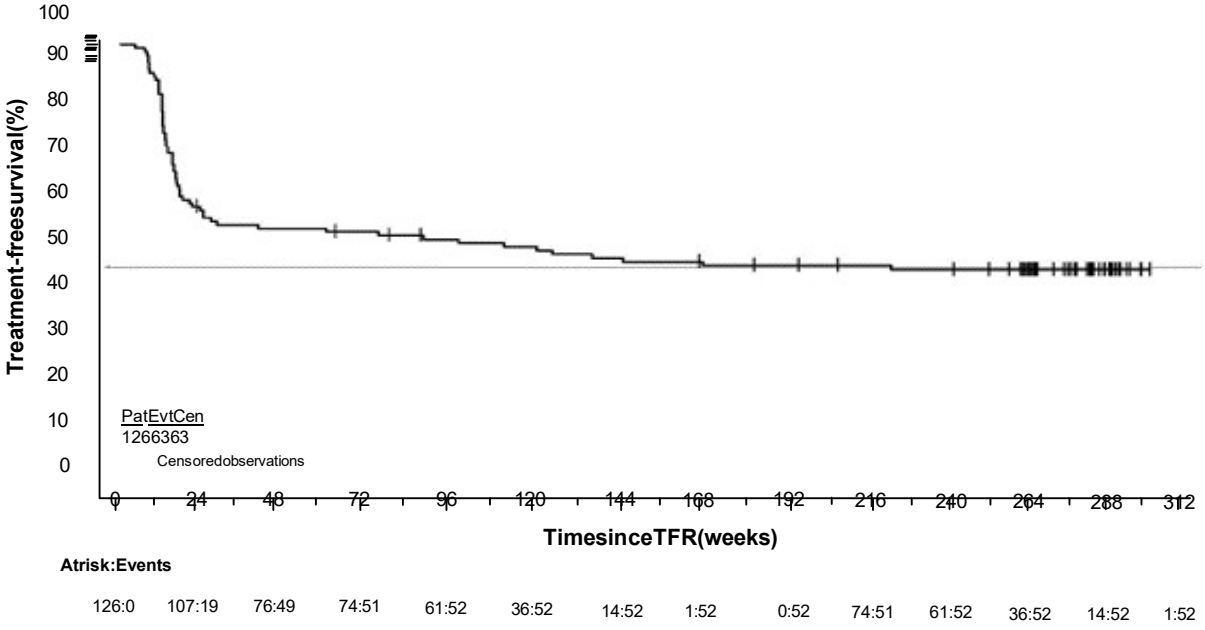
PatientsenteredTFRphase	126	
weeksafterstartingTFRphase	48 weeks	264 weeks
patientsremaininginMMR,no confirmedlossofMR4.0,andno re-initiation of nilotinib	73(57.9%,[95%CI:48.8, 66.7])	54(42.9%[54/126,95% CI:34.1,52.0])
PatientsdiscontinuedTFRPhase	53	74 [1]
duetoconfirmedlossofMR4.0or loss of MMR	53 (42.1%)	61 (82.4%)
duetoother reasons	0	13
Patientsrestartedtreatmentafterlossof MMR or confirmed loss of MR4.0	51	59
regaining MR4.0	48 (94.1%)	56 (94.9%)
regaining MR4.5	47 (92.2%)	54 (91.5%)

[1]twopatientshadMMR(PCRassessment)at264 weeksbutwerediscontinuedlaterandhadno further PCR assessment.

The Kaplan-Meier estimated median time on nilotinib to regain MR4.0 and MR4.5 was 11.1 weeks (95%CI:8.1,12.1)and13.1weeks(95%CI:12.0,15.9),respectively.ThecumulativerateofMR4and MR4.5 regained by 48 weeks after treatment re-initiation was 94.9% (56/59 patients) and 91.5% (54/59 patients), respectively.

ThemedianTFSKaplan-Meierestimateis224weeks(95%CI:39.9,NE)(Figure5); 63of 126 patients (50.0%) did not have a TFS event.

Figure 5 Kaplan-Meierestimateoftreatment-freesurvivalafterstartof TFR(fullanalysis set)



Paediatricpopulation

In the mainpaediatricstudyconducted withnilotinib, atotal of 58 patientsfrom 2to <18 years of age (25 patients newly diagnosed Ph+ CML in chronic phase and 33 patients imatinib/dasatinib-resistant or imatinib-intolerant Ph+CML inchronicphase)receivednilotinib treatment ata doseof 230 mg/m^2 twicedaily,roundedtothenearest50mgdose(toamaximum singledoseof400mg).Keystudydata are summarised in Table 13.

Table 13 Summarydataforthemainpaediatricstudyconductedwith nilotinib

	NewlydiagnosedPh+ CML-CP (n=25)	resistantorintolerantPh+ CML-CP (n=33)
Mediantimeontreatmentin month, (range)	51.9(1.4- 61.2)	60.5(0.7- 63.5)
Median(range)actualdose intensity(mg/m^2/day)	377.0(149-468)	436.9(196-493)
Relative dose intensity (%) comparedtotheplanneddose of 230 mg/m^2 twice daily Median(range) Numberofpatientswith >90%	 82.0(32-102) 12 (48.0%)	 95.0(43-107) 19 (57.6%)
MMR(BCR-ABL/ABL ≤0.1%)ISat12cycles,(95% CI)	60%,(38.7,78.9)	48.5%,(30.8,66.5)
MMRbycycle12,(95%CI)	64.0%,(42.5,82.0)	57.6%,(39.2,74.5)
MMRbycycle66,(95%CI)	76.0%,(54.9,90.6)	60.6%,(42.1,77.1)
MediantimetoMMRinmonth (95% CI)	5.56(5.52,10.84)	2.79(0.03,5.75)
No.ofpatients(%)achieved MR4.0 (BCR-ABL/ABL ≤0.01%IS)bycycle66	14 (56.0%)	9 (27.3%)
No.ofpatients(%)achieved MR4.5 (BCR-ABL/ABL ≤0.0032%IS)bycycle66	11 (44.0%)	4 (12.1%)
Confirmed loss of MMR amongpatientswhoachieved MMR	3out of19	Noneoutof 20
Emergentmutationwhileon treatment	None	None
Diseaseprogressionwhileon treatment	1patienttemporarilymatched thetechnicaldefinitionfor progression to AP/BC *	1patientprogressedtoAP/BC after10.1monthsontreatment
Overallsurvival No. of events Deathontreatment Deathduringsurvival follow up	 0 3 (12%) Notestimable	 0 1 (3%) Notestimable

*onepatienttemporarilymatchedthetechnicaldefinitionforprogressiontoAP/BC(duetoincreased basophil cell count), one month after the start of nilotinib (with temporary treatment interruption of 13daysduringfirst cycle).The patientremainedinthestudy,wentbacktoCPandwasinCHRand CCyR by 6 cycles of nilotinib treatment.

5.2 Pharmacokineticproperties

Absorption

Peak concentrations of nilotinib are reached 3 hours after oral administration. Nilotinib absorption followingoraladministrationwasapproximately30%.Theabsolutebioavailabilityofnilotinibhasnot been determined. As compared to an oral drink solution (pH of 1.2 to 1.3), relative bioavailability of nilotinib capsule is approximately 50%. In healthy volunteers, $C_{max}$and area under the serum concentration-time curve (AUC) of nilotinib are increased by 112% and 82%, respectively, compared to fasting conditions when Tasigna is given with food. Administration of Tasigna 30 minutes or 2hoursafterfoodincreasedbioavailabilityofnilotinibby29%or15%,respectively(see sections4.2, 4.4 and 4.5).

Nilotinibabsorption(relativebioavailability)mightbereducedbyapproximately48%and22%in patients with total gastrectomy and partial gastrectomy, respectively.

Distribution

Theblood-to-plasmaratioofnilotinibis0.71.Plasmaproteinbindingisapproximately98%onthe basis of *in vitro* experiments.

Biotransformation

Mainmetabolicpathwaysidentifiedinhealthysubjectsareoxidationandhydroxylation.Nilotinibis themain circulating componentinthe serum. None ofthemetabolitescontribute significantlytothe pharmacological activity of nilotinib. Nilotinib is primarily metabolised by CYP3A4, with possible minor contribution from CYP2C8.

Elimination

After a single dose of radiolabelled nilotinib in healthy subjects, more than 90% of the dose was eliminatedwithin7days,mainlyinfaeces(94%ofthedose).Unchangednilotinibaccountedfor69% of the dose.

Theapparenteliminationhalf-lifeestimatedfromthemultiple-dosepharmacokineticswithdaily dosing was approximately 17 hours. Inter-patient variability in nilotinib pharmacokinetics was moderate to high.

Linearity/non-linearity

Steady-state nilotinib exposure was dose-dependent, with less than dose-proportional increases in systemic exposure at dose levels higher than 400 mg given as once-daily dosing. Daily systemic exposuretonilotinibwith400 mgtwice-dailydosingatsteadystatewas35%higherthanwith800 mg once-daily dosing. Systemic exposure (AUC) of nilotinib at steady state at a dose level of 400 mg twice daily was approximately 13.4% higher than at a dose level of 300 mg twice daily. The average nilotinibtroughandpeakconcentrationsover12monthswereapproximately15.7%and14.8%higher following 400mgtwice-daily dosingcomparedto 300 mg twicedaily. There wasno relevantincrease in exposure to nilotinib when the dose was increased from 400 mg twice daily to 600 mg twice daily.

Steady-stateconditionswereessentiallyachievedbyday8.Anincreaseinserumexposuretonilotinib between the first dose and steady state was approximately 2-fold for daily dosing and 3.8-fold for twice-daily dosing.

Bioavailability/bioequivalencestudies

Single-doseadministrationof400mgnilotinib,using2 hardcapsulesof200mgwherebythecontent of each hard capsule was dispersed in one teaspoon of apple sauce, was shown to be bioequivalent with a single-dose administration of 2 intact hard capsules of 200 mg.

Paediatricpopulation

Following administration of nilotinib in paediatric patients at 230 mg/m^2 twice daily, rounded to the nearest 50 mg dose (to a maximum single dose of 400 mg), steady-state exposure and clearance of nilotinibwerefoundtobesimilar(within2-fold)toadult patientstreatedwith400mgtwicedaily. The pharmacokinetic exposure of nilotinib following a single or multiple doses appeared to be comparable between paediatric patients from 2 years to <10 years and from ≥10 years to <18 years.

5.3 Preclinicalsafety data

Nilotinibhasbeenevaluatedinsafetypharmacology,repeated-dosetoxicity,genotoxicity, reproductive toxicity, phototoxicity and carcinogenicity (rats and mice) studies.

Safetypharmacologystudies

Nilotinib did not have effects on CNS or respiratory functions. *In vitro* cardiac safety studies demonstrated a preclinical signal for QT prolongation, based upon block of hERG currents and prolongationoftheactionpotential durationinisolatedrabbit heartsbynilotinib.Noeffectswereseen inECGmeasurementsindogsormonkeystreatedforupto39 weeksorinaspecial telemetrystudyin dogs.

Repeated-dosetoxicitystudies

Repeated-dose toxicity studies in dogs of up to 4 weeks' duration and in cynomolgus monkeys of up to 9months' durationrevealedtheliverasthe primarytargetorgan oftoxicityof nilotinib. Alterations included increased alanine aminotransferase and alkaline phosphatase activity and histopathology findings (mainly sinusoidal cell or Kupffer cell hyperplasia/hypertrophy, bile duct hyperplasia and periportalfibrosis).Ingeneralthechangesinclinicalchemistrywerefullyreversibleafterafour-week recovery period and the histological alterations showed partial reversibility. Exposures at the lowest dose levels at which the liver effects were seen were lower than the exposure in humans at a dose of 800 mg/day. Only minor liver alterations were seen in mice or rats treated for up to 26 weeks. Mainly reversible increases in cholesterol levels were seen in rats, dogs and monkeys.

Genotoxicitystudies

Genotoxicitystudiesinbacterial *invitro*systemsandinmammalian*invitro*and*invivo* systemswith and without metabolic activation did not reveal any evidence for a mutagenic potential of nilotinib.

Carcinogenicitystudies

Inthe2-yearratcarcinogenicitystudy,themajortargetorganfornon-neoplasticlesionswastheuterus (dilatation, vascular ectasia, endothelial cell hyperplasia, inflammation and/or epithelial hyperplasia). There was no evidence of carcinogenicity upon administration of nilotinib at 5, 15 and 40 mg/kg/day. Exposures (in terms of AUC) at the highest dose level represented approximately 2x to 3x humandaily steady-state exposure (based on AUC) to nilotinib at the dose of 800 mg/day.

In the 26-week Tg.rasH2 mouse carcinogenicity study,in which nilotinib was administeredat30, 100 and 300 mg/kg/day, skin papillomas/carcinomas were detected at 300 mg/kg, representing approximately 30to 40times (basedon AUC) the human exposure at the maximum approved dose of 800 mg/day (administered as 400 mg twice daily). The No-Observed-Effect-Level for the skin neoplasticlesionswas100mg/kg/day,representingapproximately10to20 timesthehumanexposure at themaximumapproveddoseof800mg/day(administeredas400mgtwicedaily).Themajortarget organs for non-neoplastic lesions were the skin (epidermal hyperplasia), the growing teeth (degeneration/atrophy of the enamel organ of upper incisors and inflammation of the gingiva/odontogenic epithelium of incisors) and the thymus (increased incidence and/or severity of decreased lymphocytes).

Reproductivetoxicityandfertilitystudies

Nilotinib did not induce teratogenicity, but did show embryo- and foetotoxicity at doses that also showed maternal toxicity. Increased post-implantation loss was observed in both the fertility study, which involved treatment of both males and females, and the embryotoxicity study, which involved treatmentoffemales.Embryo-lethalityandfoetaleffects(mainlydecreasedfoetalweights,premature fusion of the facial bones (fused maxilla/zygomatic) visceral and skeletal variations) in rats and increased resorption of foetuses and skeletal variations in rabbits were present in the embryotoxicity studies. In a pre- and postnatal development study in rats, maternal exposure to nilotinib caused reduced pup body weight with associated changes in physical development parameters as well as reduced mating and fertility indices in the offspring. Exposure to nilotinib in females at No-Observed-Adverse-Effect-Levelswasgenerallylessorequaltothatinhumansat800 mg/day.

Noeffectsonspermcount/motilityoronfertilitywerenotedinmaleandfemaleratsuptothehighest tested dose, approximately 5 times the recommended dosage for humans.

Juvenileanimalstudies

In a juvenile development study, nilotinib was administered via oral gavage to juvenile rats from the first week post partum through young adult (day 70 post partum) at doses of 2, 6 and 20 mg/kg/day. Besidesstandardstudyparameters,evaluationsofdevelopmentallandmarks,CNSeffects,matingand fertility were performed.Based on a reduction in bodyweight inbothgendersanda delayedpreputial separation in males (which may be associated with the reduction in weight), the No-Observed-Effect-Levelinjuvenileratswasconsideredtobe6 mg/kg/day.Thejuvenileanimals did not exert increased sensitivity to nilotinib relative to adults. In addition, the toxicity profile in juvenile rats was comparable to that observed in adult rats.

Phototoxicitystudies

Nilotinib was shown to absorb light in the UV-B and UV-A range, is distributed into the skin and showedaphototoxicpotential*invitro*,butnoeffectshavebeenobserved*invivo*.Thereforetherisk that nilotinib causes photosensitisation in patients is considered very low.

6. PHARMACEUTICALPARTICULARS

6.1 Listofexcipients

Tasigna50mghardcapsules

Capsule content
Lactose monohydrate
CrospovidoneTypeA
Poloxamer 188
Colloidalanhydroussilica
Magnesium stearate

Capsuleshell
Gelatin
Titanium dioxide (E171)
Red iron oxide (E172)
Yellowironoxide(E172)

Printingink
Shellac
Blackironoxide(E172)
Propylene glycol
Ammonium hydroxide

Tasigna150mghardcapsules

Capsule content
Lactose monohydrate
CrospovidoneTypeA
Poloxamer 188
Colloidalanhydroussilica
Magnesium stearate

Capsuleshell
Gelatin
Titanium dioxide (E171)
Red iron oxide (E172)
Yellowironoxide(E172)

Printingink
Shellac
Blackironoxide(E172)
n-Butyl alcohol
Propylene glycol
Dehydrated ethanol
Isopropyl alcohol
Ammonium hydroxide

Tasigna200mghardcapsules

Capsule content
Lactose monohydrate
CrospovidoneTypeA
Poloxamer 188

Colloidalanhydroussilica
Magnesium stearate

Capsuleshell
Gelatin
Titanium dioxide (E171)
Yellowironoxide(E172)

*Printing ink*Shellac
(E904)
Dehydratedalcohol
Isopropyl alcohol
Butyl alcohol
Propylene glycol
Strongammoniasolution
Potassium hydroxideRed
iron oxide (E172)

6.2 Incompatibilities

Notapplicable.

6.3 Shelflife

3 years.

6.4 Specialprecautionsforstorage

Donotstoreabove30°C.

Storeintheoriginalpackageinordertoprotectfrommoisture.

6.5 Nature and contents of container

Tasignaisavailableinthefollowingpacksizes:

Tasigna 50 mg hard capsules

PVC/PVDC/Alublisters
Packcontaining120(3packsof40)hardcapsules.

Tasigna 150 mg hard capsules

PVC/PVDC/Alublisters
- Unitpackscontaining28hardcapsules(7dailyblisters,eachcontaining4hardcapsules)or 40 hard capsules (5 blisters, each containing 8 hard capsules).
- Multipackscontaining112(4packsof28)hardcapsules,120(3packsof40)hardcapsulesor 392(14packsof28)hard capsules.

Notallpacksizesmaybemarketed.

Tasigna200mghard capsules

PVC/PVDC/Alublisters

- Unitpackscontaining28hardcapsulesina wallet.
- Unitpackscontaining28hardcapsules(7dailyblisters,eachcontaining4hardcapsules)or 40 hard capsules (5 blisters, each containing 8 hard capsules).
- Multipackscontaining112(4walletsof28)hardcapsules.
- Multipackscontaining112(4packsof28)hardcapsules,120(3packsof40)hardcapsulesor 392(14packsof28)hard capsules.

Notallpacksizesmaybemarketed.

6.6 Specialprecautionsfordisposal

Anyunusedmedicinalproductorwastematerialshouldbedisposedofinaccordancewithlocal requirements.

7. MARKETINGAUTHORISATIONHOLDER

Novartis Nigeria Limited

The Landmark House

Plot 52-54 Isaac John Street

Ikeja GRA, Lagos
Nigeria.

8. MARKETINGAUTHORISATIONNUMBER(S)

Tasigna 200mg Capsules – A4-3031
Tasigna 150mg Capsules – B4-1923