

**Common:** anorexia, insomnia, dizziness, paresthesia, taste disturbance, hypoesthesia, flushing, photosensitivity reaction, weakness, pyrexia, chills, weight decreased, lacrimation increased, conjunctivitis, dry eye, blurred vision, dyspnea, epistaxis, cough, flatulence, abdominal distension, gastro-esophageal reflux, constipation, dry mouth, gastritis, increased hepatic enzymes, pruritus, dry skin, erythema, alopecia, night sweats, joint swelling

**Potentially serious:** fluid retention, anasarca, edema (including brain, eye, pericard, abdomen and lung), neutropenia, thrombocytopenia or anemia, pancytopenia, hemolytic anemia, hypokalemia, hyperkalemia, sepsis, cellulitis, fungal infection, upper respiratory tract infection, interstitial lung disease, pneumonia, pericardial/pleural effusion, pleuritic pain, pulmonary hypertension/hemorrhage/fibrosis, cardiac failure congestive, arrhythmia, atrial fibrillation, cardiac arrest, myocardial infarction, angina pectoris, pericarditis, cardiac tamponade, thrombosis/embolism, ileus/intestinal

obstruction, pancreatitis, hepatic failure/necrosis, hepatitis, exfoliative dermatitis, angioneurotic edema, Stevens-Johnson syndrome, erythema multiforme, leukocytoclastic vasculitis, Sweet's syndrome, lichenoid keratosis, lichen planus, toxic epidermal necrolysis, anaphylactic shock, syncope, hypotension, hematoma, acute respiratory failure, acute renal failure, hemorrhage (including brain, eye, kidney and gastrointestinal tract), melena, hematemesis, diverticulitis, colitis, inflammatory bowel disease, gastrointestinal perforation, ascites, gastric ulcer, tumour hemorrhage/necrosis, hip osteonecrosis/avascular necrosis, sciatica, optic neuritis, cataract, papilledema, glaucoma, hearing loss, Raynaud's phenomenon, increased intracranial pressure, peripheral neuropathy, depression, convulsions

**Note:** Before prescribing, please read full Summary of Product Characteristics.

## EUTOS for CML is a unique support program designed to help you optimize patient outcomes in Ph+ CML.

Under the umbrella EUTOS for CML there are 4 different projects

- Expanded CML registry
- Imatinib blood level testing program
- Standardized real-time quantitative PCR (RQ-PCR) monitoring program
- Medical education and program-support materials

### References:

1. Druker BJ, Guilhot F, O'Brien SG, et al. Five-year follow-up of patients receiving imatinib for chronic myeloid leukemia. *N Engl J Med.* 2006;355:2408-2417.
2. Picard S, Titier K, Etienne G, et al. Trough imatinib plasma levels are associated with both cytogenetic and molecular responses to standard-dose imatinib in chronic myeloid leukemia. *Blood.* 2007;109:3496-3499.
3. Tsang J-P, Rudychev I, Pescatore SL. Prescription compliance and persistency in CML and GIST patients receiving imatinib. Poster presented at ASCO 2006.
4. Imatinib (imatinib mesilate) Summary of Product Characteristics. Basel, Switzerland: Novartis Pharma AG; 2007.

PLEASE SEE ENCLOSED SUMMARY OF PRODUCT CHARACTERISTICS AND IMPORTANT SAFETY INFORMATION ON PAGES 8-9. LEARN MORE BY CONTACTING YOUR NOVARTIS ONCOLOGY REPRESENTATIVE.

# EUTOS for CML

## Optimizing patient care in CML across Europe

Introducing imatinib blood level testing from EUTOS for CML

Program subject to legal and regulatory approval.

EUTOS for CML

  
European Treatment and Outcome Study

## Imatinib blood level testing: A key management tool for Ph+ CML

The efficacy of imatinib for the treatment of Philadelphia-chromosome-positive chronic myeloid leukemia (Ph+ CML) is well established.<sup>1</sup> However, ensuring adequate imatinib trough plasma concentrations may be important for achieving the full potential benefit of the drug. Imatinib blood levels that are too low may lead to a lack of efficacy or suboptimal response.<sup>2</sup>

EUTOS for CML is offering imatinib blood level testing to physicians who treat patients with Ph+ CML with imatinib. The imatinib blood level testing program can help with patient management and help you to optimize clinical outcomes in Ph+ CML.

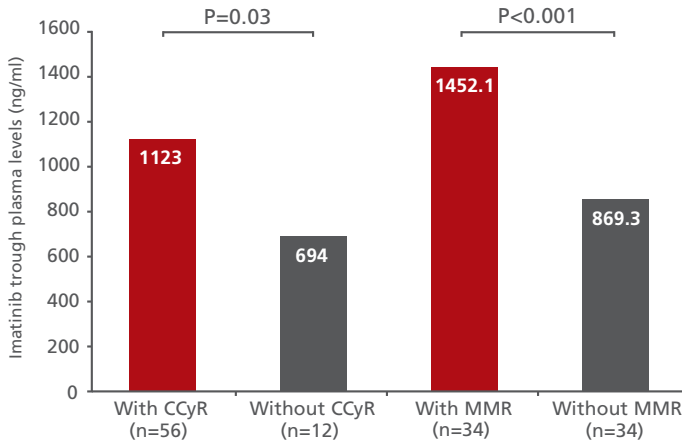
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# Imatinib trough levels have been associated with clinical response

Higher imatinib trough plasma levels have been associated with increased likelihood of achieving a complete cytogenetic response (CCyR) or major molecular response (MMR).<sup>2</sup>

- In patients treated with standard-dose imatinib, mean trough plasma levels were significantly higher in patients with CCyR or MMR than in those without CCyR or MMR, respectively<sup>2</sup>

## Mean imatinib trough plasma levels in patients with or without CCyR or MMR<sup>1</sup>



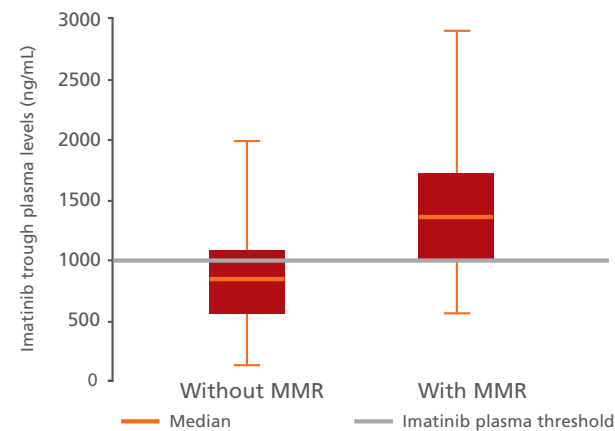
n=68. Patients with Ph+ CML in the chronic phase (CP) (n=50) and the accelerated phase (AP) (n=18) treated for  $\geq 12$  months with standard-dose imatinib (400 mg QD for CP and 600 mg QD for AP). CCyR was defined as 0% Philadelphia-chromosome-positive cells in the bone-marrow aspirate. MMR was defined as a reduction in *BCR-ABL* transcript levels of at least 3 log from a standardized baseline.

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## Imatinib trough levels above 1000 ng/mL are associated with higher likelihood of cytogenetic and molecular responses

- A plasma threshold of 1002 ng/mL was significantly associated with the presence of MMR (odds ratio 7.8; 95% CI: 2.64, 23.03;  $P < 0.001$ )<sup>2</sup>
- The majority (76%) of patients with MMR had trough plasma levels exceeding the 1002 ng/mL threshold; the majority (71%) of patients without MMR had trough plasma levels below the threshold<sup>2</sup>

### Imatinib trough plasma levels in patients with or without MMR<sup>2</sup>



n=68. Patients with Ph+ CML in the CP (n=50) and the AP (n=18) treated for  $\geq 12$  months with standard-dose imatinib (400 mg QD for CP and 600 mg QD for AP). Chart shows distribution around the median imatinib trough plasma level. Middle line represents median; bottom edge is first quartile; top edge is third quartile; error bars represent minimal and maximal values. MMR was defined as a reduction in *BCR-ABL* transcript levels of at least 3 log from a standardized baseline.

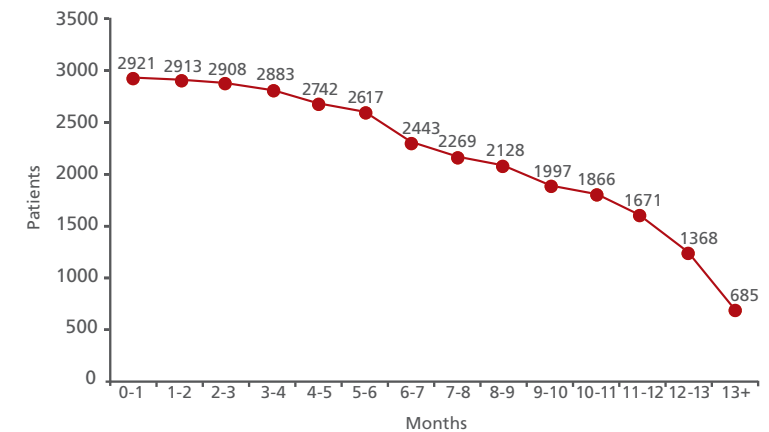
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## Declining patient adherence can be an issue with long-term oral medications

### In a 14-month US study of patients prescribed imatinib, adherence began to decline after 4 months of treatment<sup>3</sup>

- Persistency\* declined from 94% at month 5 to 23% at month 14 (n=2921)
- Persistency averaged 256 days of therapy over 12 months
- Compliance rate was 75%<sup>†</sup>

### Patients taking the recommended dose of imatinib over 14 months<sup>3</sup>



n=2921 (patients analyzed for persistency). Compliance and persistency of patients prescribed imatinib were measured over a 14-month period by analysis of patient pharmacy records to track prescriptions written vs prescriptions filled.

\*Persistency=time each patient stayed on therapy without significant gaps in refills.

†Compliance=medication possession ratio (apparent mg taken divided by mg prescribed).

## Imatinib blood level testing can help you optimize patient outcomes

Maintaining therapy with imatinib can lead to durable long-term responses.<sup>1</sup> Imatinib blood level testing can help you find out if patients do not have adequate trough levels of imatinib in their blood to achieve the desired therapeutic effect. This may help to avoid premature discontinuation or changes in therapy.

### Consider blood level testing when:

- You have concerns about lack of adherence
- The response to imatinib is less than you would expect
- Drug–drug interactions are suspected
- Side effects are unusually severe for the dose of imatinib taken

If levels are below the recommended trough plasma concentration of 1000 ng/mL, you may need to discuss the importance of adherence with your patient.

### The test results may offer a positive way to initiate an ‘evidence-based’ discussion with your patient on the importance of adherence.

If you find that patient adherence has declined due to side effects with imatinib, remember that most mild-to-moderate side effects can be managed with supportive care.

Drug–drug interactions with concurrent medications can also cause low imatinib levels—further discussion about other medications that the patient may be taking may be required.

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## EUTOS for CML provides easy access to imatinib blood level testing

((Note: Details below are an example only. CPO to adjust page according to local program specifics))

Imatinib blood level testing is available at no cost to you or your patients.

### Easy enrollment

Your local Novartis representative will be happy to provide you with the relevant forms to complete.

### Blood level testing at no cost

EUTOS for CML will provide postage-paid, express-mail envelope you can use to mail blood samples for testing. Imatinib blood level testing will be performed at the central facility in Bordeaux.

### Obtaining results

You will receive test results directly from the center in Bordeaux

EXAMPLE ONLY  
DETAILS PROVIDED AS A MODEL

### Sample Monitoring request form

**IMATINIB (GLIVEC®) MONITORING REQUEST** **EUTOS FOR CML**

**CENTRE HOSPITALIER UNIVERSITAIRE DE BORDEAUX**  
LABORATOIRE DE PHARMACOLOGIE CLINIQUE ET TOXICOLOGIE  
# M. Molliard  
Centre Hospitalier Pellegrin – Tipode  
Plateau technique 2e étage – 33076 Bordeaux Cedex, France  
Tel: +33 (0)5 56 79 59 91 – Fax: +33 (0)5 56 79 47 95

**Patient's identity:**  
Label with identifying number \_\_\_\_\_  
OR  
Surname: \_\_\_\_\_  
Matr. name: \_\_\_\_\_  
First name: \_\_\_\_\_  
Gender: \_\_\_\_\_  
Date of birth: \_\_\_\_\_

**Details of the clinical unit:**  
Telephone: \_\_\_\_\_  
Fax: \_\_\_\_\_  
Complete address and/or  
Stamp of the unit: \_\_\_\_\_

**Reminders for the sampling:**  
- JUST BEFORE INTAKE (= residual)  
- VAL: Heparinized, take plasma after  
Centrifugation

**Sampling:**  
- Date: / /  
- Hour: / /  
Last Imatinib intake:  
- Date: / /  
- Hour: / /

**FURTHER INFORMATION:**  
Name of physician: \_\_\_\_\_  
Clinical information: \_\_\_\_\_

Suspicion of non-adherence  
 Suspicion of drug-drug interaction  
 Insufficient response  
 Scheme events (please detail): \_\_\_\_\_

**Imatinib dose** Morning Mid-day Evening  
 \_\_\_\_\_

Chronic phase  \_\_\_\_\_  
Accelerated phase  \_\_\_\_\_

**Philadelphia chromosome status (p11)**  
Date of analysis: / /  
 Absence of Cytogenetic Response (100% Ph+)  
 Absence of Partial Cytogenetic Response (>25% Ph+)  
 Partial Cytogenetic Response (<25% Ph+)  
 Complete Cytogenetic Response (0% Ph+)

Associated treatments: \_\_\_\_\_

Investigation of mutations:  
 no  yes, mutation(s): \_\_\_\_\_

**Quantification of BCR-ABL transcripts**  
Date of analysis: / /  
 Absence of Molecular Response  
 Absence of Major Molecular Response (level > 0.1% or reduction of more than 3 logs)  
 Major Molecular Response (level > 0.1% or reduction of more than 3 logs)  
 Complete Molecular Response (transcripts undetectable)

**Shipment conditions:**  
PLASMA should be transferred below **+30°C** by an approved carrier

### EUTOS for CML offers resources for your practice

A comprehensive package of supporting materials and activities is in development.

This resource is designed to make it as easy as possible for you to optimize imatinib therapy through blood level testing. It includes:

- A guide to participating in the EUTOS for CML blood level testing program
- Medical education and slide kits
- Blood-level testing case studies



# Indication and important safety information

## Indication statement

Imatinib is indicated for the treatment of adult and pediatric patients with newly diagnosed Philadelphia-chromosome- (*BCR-ABL*) positive (Ph+) chronic myeloid leukemia (CML) for whom bone-marrow transplantation is not considered as the first line of treatment, and for adult and pediatric patients with Ph+ CML in chronic phase after failure of interferon-alpha therapy, or in accelerated phase or blast crisis.

## Important safety information<sup>4</sup>

**Contraindications:** Hypersensitivity to imatinib or to any of the excipients

**Precautions/Warnings:** Should be taken with food and a large glass of water to minimize the risk of gastrointestinal disturbances. Beware of severe fluid retention. It is recommended that patients be weighed regularly. Regular monitoring of complete blood counts and liver function tests. Caution in patients with history of cardiac disease. Careful monitoring of patients with cardiac

disease or risk factors for cardiac failure. Monitoring of TSH levels in thyroidectomy patients undergoing levothyroxine replacement. Should not be used during pregnancy unless clearly necessary. Should not be used by breast-feeding mothers

**Interactions:** Caution with CYP3A4 inhibitors (e.g. ketoconazole, clarithromycin). Caution with CYP3A4 inducers (e.g. dexamethasone, rifampicin, phenytoin, carbamazepine, phenobarbital, St. John's Wort). Caution with substrates of CYP3A4 (e.g. triazolo-benzodiazepines, dihydropyridine calcium channel blockers, simvastatin, cyclosporin, pimozone), CYP2C9 (e.g. warfarin) or CYP2D6 (e.g. metoprolol). Caution with concomitant use of paracetamol/acetaminophen

## Adverse reactions:

**Very common:** headache, nausea, vomiting, diarrhea, dyspepsia, abdominal pain, myalgia, arthralgia, muscle spasm or cramps, bone pain, dermatitis, eczema, rash, fatigue, weight increase

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