Imatinib as first TKI to become generic: What we need to know about generics in cancer therapy

Generics have been part of the prescriptions in cancer therapy for quite some time now. And the numbers grow: According to recent figures mentioned in *Cancer World*[1], in a total global oncology drugs market approaching $100 billion, revenues from generics are growing at twice the rate of the market as a whole. They will reach more than $20 billion by 2018.

Now one of the first targeted therapies, Imatinib (Glivec®/Gleevec®), becomes generic: The patent expired or will expire for the treatment of Chronic Myeloid Leukaemia (CML) in different countries. Even though the patent for Imatinib in GIST isn't running out until approximately 2021, generic Imatinib might be offered to GIST patients as well. That is why we want to provide you with some valuable background information about generics and answer some of the questions you might have.

First of all, we need to be clear about the terminology and define the differences between a generic drug, a copy drug, a substandard drug and a counterfeit drug:[2]

Generic drug

- A product that is comparable to innovator drug product (also called "brand name") in dosage form, strength, route of administration, quality and efficacy, and intended use. A generic drug can only be marketed after patent & exclusivity protection of the original ends.

Copy drug

- Drug provided by third party manufacturers despite the drug is still patented

Substandard drug

- A "genuine" drug product
- Does not meet quality specifications
- Due to difference in isoforms, isomers & impurities, may lead to lack of therapeutic equivalence

Counterfeit drug

- Deliberately and fraudulently mislabeled
- Can apply to branded or generic drugs
- Includes products with correct or wrong ingredients, without active ingredients, with insufficient active ingredients, with fake packaging

How is a generic drug authorized?

According to EMA, "a generic medicine contains the same active substances as the reference medicine [e.g. Glivec®/Gleevec®], and it is used at the same doses to treat the same diseases. However, a generic medicine's inactive ingredients, name, appearance and packaging can be different from the reference medicine's. Generic medicines are manufactured according to the same quality standards as all other medicines."[3]

Generic drugs must undergo a rigorous quality control process before they can obtain marketing authorization by a regulator such as the European Medicines Agency (EMA) in Europe or the Food and Drug Administration (FDA) in the U.S. This includes a scientific evaluation of the medicine's **efficacy** (how well it works as measured in clinical studies), **safety** and **quality**.[3]

As the reference medicine will have been authorized for several years, information is already available on the **efficacy and safety** of the active substance(s) it contains. Therefore, the manufacturer has to prove that the generic medicine is comparable to the reference medicine in order to receive marketing authorization. He also needs to provide information on the quality of the medicine: For drugs taken orally, the pharmaceutical company will need to supply data from a **bioequivalence study** to show that the generic medicine produces the same levels of the active substance in the body (whether human or animal) as the reference medicine.[3]

What is bioequivalence?

"Bioavailability" refers to the rate and extent of absorption of an active ingredient from a drug product so that it becomes available at its site of action.

"Bioequivalence" means that the active ingredient of two drug products has the same rate and extent of absorption. When it acts on its target (e.g. receptor on the tumor) the brand-name and the generic drug should deliver the same amount of active ingredient to the target site. [4]

Two related drugs are bioequivalent if they show comparable bioavailability and similar times to achieve peak blood concentrations.

How can bioavailability be assessed?

There are different ways of assessing *bioavailability*. The most common method is to conduct a pharmacokinetic study, in which the drugs are given orally. Then the scientists measure how much of the active ingredient of the medication is actually absorbed and detectable in the bloodstream. This can be done by collecting blood samples at different time points after administration.[4]

For a generic drug to be considered bioequivalent, it should meet 90 percent confidence intervals of 80 to125 percent test reference ratio. Significant difference is 20% ($\alpha = 0.05$ significance level). This simply means that the generic's bioavailability is not significantly less than the brand name and vice versa.[5]

Bioequivalent products can be substituted for each other without any adjustment in dose or other additional therapeutic monitoring

But careful: Bioequivalence does not necessarily mean therapeutic equivalence. To be therapeutically equivalent, a drug should have the same clinical effect and safety profile. These are not demonstrated in a bioequivalence test.[5]

How can generics differ from innovator drug products?

Even though the generic needs to have the same active ingredient (mode of action, amount, safety, efficacy, pharmacokinetic & pharmacodynamic properties, purity and stability), the same therapeutic indication and route of administration, it may differ in shape, size and scoring, manufacturing process and product name and packaging. Moreover, the usage of different salts and excipients (colors, flavors and preservatives) is allowed. If they differ significantly in their safety and/or efficacy properties, the generic manufacturer has to submit further proof of efficacy and safety.[2]

Once the generic medicine is authorized, the same information will appear in the 'product information' of the generic medicine (the summary of product characteristics, the labelling and the

package leaflet) as in the product information of the reference medicine. The only differences relate to any differences in excipients and any patented indications. If precautions are necessary because of an excipient, they will be described both on the label and in the package leaflet of the generic medicine. If the reference medicine is benefiting from patent protection for some indications, these cannot appear in the product information of the generic medicine.[3] The latter will be the case for Glivec®/Gleevec®, which will only lose it's patent in CML, not in GIST.

What does this mean for the patients?

In general, generics are a good thing because they improve patient access to more affordable therapies in many countries and offer relieve to national healthcare systems. However, patients also have a lot of questions and are uncertain about the impact on their cancer when switched between different products for non-medical reasons.

Questions you might have:

1. Do generics take longer to act in the body?

No. The firm seeking to sell a generic drug must show that its drug delivers the same amount of active ingredient in the same timeframe as the original product.

2. Are generics as potent as brand-name drugs?

Regulators as the European Medicines Agency (EMA) or the Food and Drug Administration (FDA) require generics to have the same quality, strength, purity, and stability as innovator drugs – therefore: yes, they should be just as potent.

3. Are Generics as safe as brand-name drugs?

The EMA and the FDA requires that all drugs be safe and effective and that their benefits outweigh their risks. Since generics use the same active ingredients and are shown to work the same way in the body, they have the same risk-benefit profile as their brand-name counterparts.

4. Brand-name drugs are made in modern manufacturing facilities, and generics are often made in substandard facilities – is that true?

No. Neither EMA nor FDA permit drugs to be made in substandard facilities. FDA conducts about 3,500 inspections a year in all firms to ensure standards are met. Generic firms have facilities comparable to those of brand-name firms. In fact, brand-name firms account for an estimated 50 percent of generic drug production. They frequently make copies of their own or other brand-name drugs but sell them without the brand name.

5. Are Generic drugs likely to cause more side effects?

There is no evidence of this. Both EMA and FDA monitor reports of adverse drug reactions and have found no difference in the rates between generic and brand-name drugs.

What you should keep in mind

Since most generic drugs carry a lower price than the brand name equivalent, cost will be an important factor for GIST patients being switched to generics even though the patent has expired for CML, not for GIST. Lower cost does not mean lower quality, but consumers should monitor information about the generic form of their medication with their physician and medical teams.

The CML community has been surveying the development imatinib generics very closely for a couple of years now. They have come up with a declaration calling to governments, health authorities and healthcare professionals to minimize potential uncertainties and risks for patients. Some aspects are very important for GIST patients being switched to a generic:

- A patient should not be switched between products with the same compound for non-medical reasons, provided this patient already responds optimally to the current product and tolerates it well.
- If a switch for non-medical reasons between products with the same compound is enforced, this should not happen more frequently than once in a year, to allow a consistent follow-up of responses and side effects on the same treatment. If a patient loses its response or experiences a significant increase of toxicities after switching to the other product, the patient must have the option to return to the previous treatment, or switch to another treatment if available.
- After switching between products with the same compound, more frequent monitoring should be conducted to detect potential differences in effectiveness or side effects early.

The whole declaration can be viewed on the CML Advocates Network website:
http://www.cmladvocates.net/news/133-generics/354-chronic-myeloid-leukemia-patients-call-for-quality-and-consistency-when-generics-are-introduced-to-treat-their-cancer

In case you're switched to a generic, there are three things we would urge you to do:

- Stay in close contact with your doctor/your medical team and discuss options/changes.
- Keep in touch with other patients in the same situation and exchange thoughts and experiences.
- Monitor yourself closely and don't hesitate to contact your doctor if you experience any changes.

Further information:

- All generics currently approved by the EMA can be viewed here: http://www.ema.europa.eu/ema/index.jsp?curl=pages%2Fmedicines%2Flanding%2Fepar_search.jsp&mid=WC0b01ac058001d124&searchTab=searchByKey&alreadyLoaded=true&isNewQuery=true&status=Authorised&keyword=imatinib&keywordSearch=Submit&searchType=inn&taxonomyPath=&treeNumber=&searchGenericType=generics
- The Life Raft Group offers a variety of material about generics: https://liferaftgroup.org/generics/
- EMA: Q&A about Generics: http://www.ema.europa.eu/docs/en_GB/document_library/Medicine_QA/2009/11/WC500012382.pdf
- CML Advocates Network offers extensive information about generics in CML (Glivec®/Gleevec®) on their website: http://www.cmladvocates.net/generics

[1] Cancer World, Jan-Feb 2015. Online on: http://www.cancerworld.org/Articles/Issues/65/March-April-2015/Systems--Services/708/Generic-cancer-drugs-that-we-can-trust.html. Last accessed February 2016.
[2] Life Raft Group, 2015. Online on: https://liferaftgroup.org/science-of-generics/. Last accessed February 2016.
[3] European Medicines Agency, 2012. Online on: http://www.ema.europa.eu/docs/en_GB/document_library/Medicine_QA/2009/11/WC500012382.pdf. Last accessed February 2016.
[4] Lowers J, Howland RH. Medscape, April 2013. Online on: http://www.medscape.com/viewarticle/762343_2. Last accessed February 2016.
[5] Life Raft Group, 2016. Online on: https://liferaftgroup.org/2016/02/generic-imatinib-available-in-the-us/. Last accessed February 2016.