

## 3 Patented medicines included in the EML: *Case study on medicines for chronic myeloid leukaemia*

### 3.1 Background

New, patented medicines have been added to the WHO EML in each of its recent revisions. Beyond HIV, HCV, and TB, other patented medicines that have recently been added to the EML have been primarily for the treatment of certain cancers, hepatitis B or for reproductive health. Two cancer medicines on the WHO EML have compound patent protection and, unless licensed to generic manufacturers, are unlikely to become available as generics in LMICs until those patents expire. In this case study, we examine the case for MPP licensing of these two medicines – dasatinib and nilotinib – which were added to the WHO EML in 2017 as second-line treatments for chronic myeloid leukaemia.<sup>1,2</sup> Some other cancer medicines in the EML that still have secondary patent protection in certain countries are discussed in Chapter 8.

### 3.2 Burden of disease in low- and middle-income countries

Chronic myeloid leukaemia (CML) is a condition in which a type of stem cell begins to proliferate uncontrollably. This process suppresses the normal development of blood cells, leading to fatigue, anaemia and spleen enlargement.<sup>3</sup> Other initial symptoms of CML include fever, abdominal pain and a feeling of fullness, and pain in the bones.<sup>4</sup> Before the advent of newer medicines called tyrosine kinase inhibitors (TKIs), the expected survival time for CML was five to seven years.<sup>5</sup> With TKI treatment, it is estimated that survival time may now be more than 25 years.<sup>3</sup> In 2015, there were 106,000 prevalent cases of CML in countries included in past MPP licences. There were a further 83,000 people with CML in other upper middle-income countries.<sup>6</sup> We project that prevalence in countries included in past MPP licences will increase to 147,000 by 2030 and incidence will increase to 32,000 (appendix).

In 85–90% of cases, CML is caused by a mutation in chromosome structure, with the resulting altered chromosome known as the Philadelphia chromosome.<sup>7</sup> This altered chromosome produces a mutated tyrosine kinase enzyme which leads to uncontrolled cell growth. Imatinib, the first drug that could selectively inhibit this mutated enzyme and thus control the disease, was developed in the 1990s,<sup>8</sup> and added to the WHO EML in 2015.<sup>2</sup> Newer medicines in the same class are termed second-generation TKIs (SG-TKIs), which include dasatinib and nilotinib. These newer medicines are the focus of the analysis presented in this chapter.

In the US, the median age at presentation for CML is 55 to 65 years.<sup>9</sup> In high-income countries, CML is generally diagnosed as an incidental finding before it has become symptomatic, while undertaking a blood sample analysis.<sup>4</sup> Studies have suggested that the median age of presentation may be 20 years lower in Africa and Pakistan compared to high-income countries.<sup>10,11</sup> However, in India, it is unusual for CML cases to be diagnosed while they are still asymptomatic – they are usually diagnosed when the disease is already more advanced.<sup>12–14</sup> A similar pattern is reported in Nigeria.<sup>15</sup> This

later presentation of CML in resource-poor settings is likely due to the lower rate of full blood count testing compared to high-income countries.

National background papers commissioned to inform this feasibility study suggest that the proportion of cases that are diagnosed is as low as 30% in Kenya, Haiti and Botswana, while local experts in Pakistan and Uzbekistan reported diagnosis rates may be more than 90%. Without more systematic data, these numbers need to be interpreted with caution.

### 3.3 Note on acute lymphocytic leukaemia

In addition to use as second-line therapy in CML, dasatinib is also indicated for acute lymphocytic leukaemia (ALL) when it displays the Philadelphia mutation (Ph+ ALL).<sup>16</sup> There were 439,000 people living with ALL in countries included in past MPP licences in 2015,<sup>6</sup> of which about 70,000 are estimated to be Philadelphia chromosome positive.

About 60% of cases of ALL occur in people less than 20 years of age,<sup>17</sup> and about 16% of cases display the Philadelphia chromosome mutation. In broad terms, ALL manifests with symptoms similar to those in CML. However, these symptoms usually present suddenly in ALL, as opposed to slowly emerging in CML.<sup>18</sup> In high-income countries, when optimal treatment is given, survival rates for ALL are excellent.<sup>19</sup> A subset of ALL has a significantly worse prognosis (unless treated with TKIs), with up to 75% of those affected dying within a year.<sup>20</sup>

Imatinib is approved for the first-line treatment of Ph+ ALL and dasatinib is approved for second-line treatment of Ph+ ALL. Dasatinib has been shown to be efficacious in Ph+ ALL as first- or second-line treatment, in combination with chemotherapy.<sup>20</sup> There is evidence that nilotinib is also effective in Ph+ ALL, though it is not licensed for this use.<sup>21</sup> While this chapter focuses mainly on CML, the impact analysis below also considers the possible use of dasatinib for the treatment of ALL.

### 3.4 Outline of drugs, diagnostic methods and guidelines

Imatinib, dasatinib and nilotinib are all approved for the first-line treatment of CML.<sup>22</sup> However, dasatinib and nilotinib were included in the EML due to their importance as second-line treatments, which therefore remains the main focus of this chapter.

While imatinib is a highly effective medicine, an estimated 23% (or 40% according to the UK National Institute for Health and Care Excellence) of patients with CML may eventually become resistant or intolerant to standard-dose imatinib.<sup>23,24</sup> Treatment options for imatinib-resistant CML include high-dose imatinib (300-400mg twice daily, as opposed to the normal dose of 400mg once daily), dasatinib, or nilotinib.<sup>22</sup>

European and US guidelines recommend all three treatments as second-line therapies.<sup>25,26</sup> However, dasatinib and nilotinib may offer multiple benefits to high-dose imatinib. US guidelines consider that patients with primary resistance to imatinib are unlikely to benefit from dose escalation and a SG-TKI should be used.<sup>26,27</sup> In addition,

trials have suggested that an earlier, rather than later, switch to SG-TKIs results in better patient outcomes.<sup>22</sup>

SG-TKIs have shown greater efficacy compared to imatinib *in vitro* and have shown larger responses in proxy measures of disease activity.<sup>28</sup> So-called ‘deep molecular responses’ are more frequently achieved with dasatinib or nilotinib compared to high-dose imatinib. Deep molecular response is associated with better event-free survival, transformation-free survival, and failure-free survival.<sup>22,29–32</sup> The risk of transformation from chronic phase to accelerated or blast phase leukaemia is decreased in patients taking dasatinib or nilotinib rather than imatinib<sup>E,24</sup> Dasatinib and nilotinib are also considered to have favourable side effect profiles compared to imatinib.<sup>22,23</sup>

Modelling exercises undertaken for the UK National Institute for Health and Care Excellence (NICE) estimated that quality adjusted life years (QALYs) and overall survival gain conferred by dasatinib and nilotinib were greater than those conferred by high-dose imatinib, and that dasatinib and nilotinib are better tolerated overall than imatinib in terms of side effects.<sup>23,33</sup>

Two other TKIs have been approved for the treatment of CML: bosutinib and ponatinib.<sup>25,26</sup> These medicines were not considered by the WHO Expert Committee for inclusion in the EML. We therefore do not focus on them. However, some of the conclusions may be equally applicable to bosutinib and ponatinib.

### 3.4.1 Diagnosis and monitoring of chronic myeloid leukaemia

Various modalities exist to diagnose and monitor CML. Cytogenetic analysis, the oldest method, requires a bone marrow sample, which is collected through a painful procedure in which a special needle is placed into the hip bone. Newer techniques can diagnose Ph+ CML using a blood sample, termed FISH and PCR<sup>F</sup>.

In sub-Saharan Africa, significant challenges exist in diagnosing haematological malignancies due to a lack of laboratories, equipment, and skilled staff.<sup>34</sup> In India, cytogenetic analysis costs US\$8–15, FISH costs US\$31–46, and PCR costs US\$77–108, per test.<sup>14</sup> GeneXpert machines, initially developed and distributed through health systems to diagnose multidrug-resistant TB, can be used to detect Ph+ CML. Public health experts hope the technology will make diagnosis easier and affordable in the near future.<sup>34–37</sup>

National background papers commissioned to inform this feasibility study noted that in Haiti, molecular testing to diagnose Ph+ CML relies on sending bone marrow out of the country, although GeneXpert machines are being repurposed for Ph+ CML diagnosis. Diagnosis by FISH is available in Botswana. In Kenya diagnosis is performed through cytogenetic testing and/or PCR, which is partially supported by the Glivec International Patient Assistance Program (now called *CMLPath to Care*; more on this below). FISH and PCR are available in Uzbekistan.

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<sup>E</sup> In patients with non-low Sokal risk scores.<sup>25</sup> In a study of Indian CML patients, 79% had non-low Sokal scores.<sup>51</sup>

<sup>F</sup> FISH – fluorescent in situ hybridisation. PCR – reverse transcriptase polymerase chain reaction.

The major modalities of monitoring CML response to treatment are cytogenetic response, requiring bone marrow sampling, and molecular response, which uses simple blood samples. Both are proxy measures for clinical outcomes.<sup>25</sup>

### 3.4.2 Availability and affordability of medicines

Data on access to dasatinib and nilotinib in LMICs is sparse. In India, it has been noted that in most large centers “patients who experienced treatment failure with imatinib are now back to receiving older medicines, such as hydroxyurea”.<sup>14</sup> A study in Rwanda noted that monitoring of CML patients receiving imatinib “had little practical implication given that if resistance to imatinib had developed, other treatment options were not available”.<sup>36</sup> During consultations with certain governments, dasatinib and nilotinib were mentioned among the medicines for which high prices are challenging for access. In some cases, this made their inclusion in NEMs difficult.

National background papers commissioned to inform this feasibility study showed highly varied availability between countries. There are originator access initiatives in place for imatinib and, to a lesser extent, nilotinib and dasatinib, which provide free or discounted access to these medicines for patients in some LMICs and have contributed to making them accessible (see section 3.9). Where originator access initiatives were not in place, the drugs were either unavailable or available on the private market at high prices (Table 1). In Botswana, while generic imatinib has recently been registered, access to SG-TKIs is costly and, given the small number of patients, effective price negotiations could be challenging. In Haiti, dasatinib is theoretically available through donations. However, mutational testing for resistance to first-line agents is currently unavailable. In Pakistan there is partial support through an originator access program. In South Africa, only nilotinib appears to be available in the public sector, at US\$156 per month. On the Indian private market, nilotinib is currently priced at US\$3,742 per month,<sup>38</sup> and dasatinib at US\$2,843 per month.<sup>39</sup>

**Table 1. Prices and availability of dasatinib and nilotinib in selected countries.**

Medicine	Price per month (USD)	
	Dasatinib	Nilotinib
Botswana	N	No data
Haiti	N	N
Kenya	Originator donated through GIPAP, no generic available	\$2,260
India	\$2,842	\$3,742
Pakistan	\$489**	\$4,341 (partial GIPAP support)
South Africa	\$1,650 (private), not available in public sector	\$156 (public), \$2,160 (private)
Uzbekistan	N	Originator donated through GIPAP, no generic available
Viet Nam	N	Originator donated through GIPAP, no generic available

**N – not registered and/or unavailable. GIPAP – Glivec International Patient Access Programme, recently replaced by CMLPath to Care. \*\*Available but not registered. Assumed dosage: imatinib 400mg/day, dasatinib 100mg/day (price for Pakistan approximated based on price for 140mg tablets), nilotinib 800mg/day.**

### 3.5 Tyrosine kinase inhibitors for CML and the WHO Expert Committee

Imatinib was first submitted for inclusion in the WHO EML in 2013 and eventually added in 2015.<sup>2,40</sup> At the time imatinib was first submitted, the medicine was still under patent in several LMICs.<sup>41</sup> In 2017, the WHO Expert Committee added dasatinib and nilotinib to the WHO EML as second-line therapies for Ph+ CML, noting that they confer “a relevant clinical benefit resulting primarily from large response rates (i.e. complete cytogenetic response) in patients with otherwise very limited treatment options”.<sup>1</sup>

### 3.6 Inclusion in national essential medicines lists (NEMs)

Of the 25 recent NEMs from LMICs that we were able to review, imatinib was included in those of Colombia, Peru, Kenya, Costa Rica, the Dominican Republic, Russia, South Africa, Panama, India and Serbia, as well as in Mexico’s reimbursement list.

Dasatinib was included in the NEMs of Peru, Thailand, Bulgaria, Croatia, Jordan, Russia and Panama.

Nilotinib was included in the NEMs of Mexico, Thailand, Bulgaria, Jordan, Russia, South Africa, Syria, Panama and Serbia.

### 3.7 Patent landscape for second-generation tyrosine kinase inhibitors

While the primary patent for imatinib expired in 2013, secondary patents on imatinib are in force until 2018/21, which may delay access to generics in countries where those patents are granted. The expiry dates for the primary patent on dasatinib and nilotinib are 2020/24 (depending on the country) and 2023 respectively. Secondary patents on these medicines may provide exclusivity until 2025-2030 and could delay generic market entry in certain countries. As shown in the table below, patents have been granted in key countries of manufacture such as India, China, and South Africa, including many of the secondary patents.

**Table 2. Patent status of CML drugs in some LMICs and expected expiry dates.**

CML	Expected date of expiry	ARIPO	BRA	CHN	EAPO	GTM	IDN	IND	MAR	OAPI	PHL	TTHA	UKR	ZA	VNM
<b>Imatinib</b>															
Product patent	2013	.	.	.	.	.	.	.	.	.	.	.	.	.	.
β-Crystalline form of Imatinib Mesylate	2018	.	F	G	G*	.	G	R	.	.	G	G	.	G	G
Method of treating gastrointestinal stromal tumours	2021	.	F	G	G*	?	.	.	?	?	G	.	?	G	.
<b>Nilotinib</b>															
Product patent	2023	.	G	G	G*	.	.	G	.	.	G	G	.	G	G
Nilotinib Monohydrochloride salt	2026	.	F	G	G*	G	F	O	G	.	G	F	.	G	.
Method of treating proliferative disorders with nilotinib.	2030	.	F	G	F*	F	G	F	G	.	G	A	.	G	.
<b>Dasatinib</b>															
Dasatinib product	2020/2024	.	F	F	F*	.	.	G	.	.	G	F	G	G	G
Crystalline Dasatinib monohydrate	2025	.	F	G	G*	.	.	O	.	.	F	.	.	G	G

*G – granted. F – filed. R – refused. \* – in Russia only. Blank – not filed. ? – no data. ARIPO – African Regional Intellectual Property Organization, EAPO – Eurasian Patent Organization, OAPI – Organisation Africaine de la Propriete Intellectuelle.*

### 3.8 Relevant market analysis for generic manufacturer interest in the area

With the expiry of the primary patent on imatinib, a number of generic manufacturers have entered the Indian market and other LMICs. However, patients with CML that eventually develop resistance or intolerance to imatinib would benefit from switching to SG-TKIs such as dasatinib and nilotinib, neither of which currently have generic versions available on the market. Nine generic manufacturers have submitted data on the active pharmaceutical ingredient to the US FDA for dasatinib, and eight for nilotinib, suggesting that several companies eventually plan to apply for approval for a generic version.<sup>42</sup> Some of these submissions are from manufacturers that have an established relationship with the MPP as generic partners and have been actively supplying LMICs with medicines for HIV and hepatitis C.

Market analyses estimate that about half of the high-income country market in value terms will comprise second- and third-generation CML drugs in 2020, with the other half comprising generic imatinib.<sup>43</sup> Similar projections are not available for LMICs, and will likely depend on price, generic market entry and originator access programmes. Originator nilotinib is currently priced at US\$3,742 per month on the Indian private market, and dasatinib at US\$2,843 per month. Generic prices in LMICs could vary significantly based on a number of factors, including volumes, which in the case of these medicines will remain low. In Tamil Nadu, imatinib is procured for \$8 per patient per month via state tender.<sup>44</sup>

Medicines with lower dosage can often have a significant price advantage over generic medicines that have higher API cost requirements.<sup>45</sup> Dasatinib has notably lower dosage (100mg daily) than nilotinib (400mg daily) and high-dose imatinib (600-800mg daily). This may mean that generic dasatinib could eventually be less expensive, as less API is needed per tablet.

### 3.9 Initiatives by originators to improve access to SG-TKIs in LMICs

Novartis, the originator company for imatinib, has partnered with the Max Foundation, a non-governmental organisation, to operate a donation scheme for imatinib – previously called the Glivec International Patient Assistance Program (GIPAP), now CMLPath to Care. The programme “[makes] imatinib accessible to all medically and financially eligible patients within 80 countries on an ongoing basis as long as their physicians prescribe it and no other means of access exists”.<sup>46</sup> In India, 55% of diagnosed patients receive imatinib through CMLPath to Care at free or a reduced price.<sup>47</sup> For nilotinib and dasatinib, access through this programme appears to be more limited. CMLPath to Care provides nilotinib for second-line treatment in a subset of those countries in which it provides imatinib. Many lower-middle income countries in Sub-Saharan Africa, Asia and Latin America are not covered.<sup>48,49</sup> At present, the program is expected to run until 2021.<sup>48</sup>

In Pakistan, Novartis has partnered with provincial governments. In four provinces, the agreements entail Novartis covering the cost of imatinib for nine months and of nilotinib for 11 months, with the provincial government then covering a further three months of treatment with imatinib, and one month with nilotinib. Two other provinces have a different agreement, where both Novartis and the provincial government partially cover the price of imatinib and nilotinib, but the patient must pay 20-50% of the price as well as laboratory monitoring costs. This latter programme experiences a higher rate of non-compliance, presumed to be due to higher out-of-pocket expenses.<sup>6</sup>

Dasatinib is also donated to the Max Foundation by the originator Bristol Myers-Squibb for specified countries. The initiative is “designed to respond to spontaneous requests for treatment access on behalf of patients who are uninsured and underinsured, where product is either not available commercially, where significant access hurdles exist and where local market initiatives cannot enable access to the therapy”.<sup>50</sup> The Max Foundation also donates GeneXpert diagnostic equipment to selected countries.<sup>49</sup>

### 3.10 Estimated public health impact for MPP intervention in SG-TKIs

Potential economic and public health impacts of hypothetical MPP licences on SG-TKIs inhibitors were estimated using the methodology outlined in Chapter 2 and described in more detail in the appendix. The assumed duration of impact was five years and we modelled low-uptake and high-uptake scenarios. See the appendix for further details.

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<sup>6</sup> Details on these programmes in Pakistan are drawn from a background paper commissioned to inform this feasibility study.

**Table 3. Estimated public health impact for MPP intervention in SG-TKIs in imatinib-resistant Ph+ CML.**

	Dasatinib	Nilotinib
<b>Total duration of impact</b>	5 years	
<b>Total patient-years of treatment</b>	42,000–150,000	17,000–124,000
<b>Total life-years gained (calculated only for treatment of imatinib-resistant Ph+ CML)</b>	5,000–33,000	3,000–19,000

### 3.11 Estimated economic impact for MPP intervention in SG-TKIs

We estimated that total theoretical savings in countries included in past MPP licences could range between US\$0.2–1.6 billion (ranges represent low- and high-uptake scenarios). Economic savings took into account the donation programmes in place for dasatinib and nilotinib in a number of LMICs.

### 3.12 Conclusions

While CML is a relatively uncommon type of cancer, it can be treated with effective oral medicines to achieve nearly normal life expectancy.<sup>3</sup> SG-TKIs such as dasatinib and nilotinib are preferable to imatinib in patients that have primary imatinib resistance, and in patients intolerant to normal-dose imatinib, and show superiority in proxy measures that are likely to translate into clinical benefits.<sup>22,25,26</sup>

We estimated that an MPP licence on SG-TKIs could potentially deliver up to 150,000 patient-years of treatment in countries included in past MPP licences over a period of five years.

While the focus of this chapter has been primarily on dasatinib and nilotinib in second-line treatment, SG-TKIs may also be used in first-line treatment and may be preferable to imatinib in patients with a high risk of progression (reported to be high in a study in India<sup>51</sup>). In addition, dasatinib, and possibly nilotinib may become important first-line therapies for ALL too. We did not consider bosutinib or ponatinib, but they may also merit further analysis.

Various factors may limit the potential impact of a hypothetical MPP license on SG-TKIs. In particular, the market for SG-TKIs is small and spread thinly across LMICs, which may limit its attractiveness for generic manufacturers, until they are able to simultaneously supply more profitable markets in high-income countries. There are, however, several manufacturers that are developing these medicines and have expressed interest in supplying LMICs.

Despite these challenges, lessons can be drawn from the case of imatinib in LMICs. Despite the small market, several manufacturers developed generic versions in India many years before generics reached high-income countries, resulting in significant price reductions.<sup>52</sup> The Indian state of Tamil Nadu, for example, procures imatinib for \$8 per patient per month.<sup>44</sup>



The donation programmes established by the originator companies in partnership with the Max Foundation have played an important role in facilitating access to treatment and diagnostics for CML in certain countries and could provide a springboard for transitioning towards what could be a more sustainable access model in the future. Discussions with all parties would be important to determine opportunities and challenges.

As with imatinib, nilotinib and dasatinib are small molecules that could be manufactured at relatively low cost and several manufacturers are developing generic versions of these medicines. MPP licences could potentially provide early access in certain LMIC markets. This could enable more people to have access to two highly effective essential medicines for cancer.

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