

Global supply of artemether-lumefantrine before, during, and after the Memorandum of Understanding between WHO and Novartis

(Report completed in May 2011)

Summary

After the agreed period of 10 years, the Memorandum of Understanding (MoU) between WHO and Novartis Pharma AG for the supply of Coartem® at cost price to malaria endemic countries has come to its end. During the time span of this MoU:

- More than 400 million treatment courses of Coartem® were supplied to malaria-endemic countries and prices were reduced by 43 - 60% over the same period. In 2010, artemether-lumefantrine accounted for more than 70% of overall ACT¹ supplies to the public sector.
- The Coartem® price offer set by the WHO-Novartis agreement was progressively extended to 18 procurement agencies.
- Three generic manufacturers of artemether-lumefantrine have been prequalified by WHO, increasing the availability of this life-saving medicines at competitive prices .

In view of the termination of the MoU on 22 May 2010 the WHO Global Malaria Programme (WHO/GMP) made a survey on planned production of all four suppliers currently manufacturing WHO-prequalified artemether-lumefantrine. The most likely market supply scenarios for this medicine indicate that production will meet the annual demand in 2011 and 2012. Due to the dynamic nature of the market and its dependence on agricultural supplies, a reassessment of the supply situation should also be performed in 2012.

1. Before May 2001: Pre-ACT Period

Plasmodium falciparum developed resistance to all antimalarial medicines used as 1st-line treatment against it, including chloroquine and SP, the safest and least expensive therapies. In the late 1990s, resistance resulted in increased severe morbidity and malaria mortality. Hence, a new approach was required, one that not only targeted the disease itself but also aimed at reducing the parasite's ability to develop resistance. For this purposes, in November 2000, WHO recommended the deployment of artemisinin-based combination therapies (ACTs) for the treatment of uncomplicated falciparum malaria. By April 2001, WHO recommended four effective ACTs with potential for large-scale implementation: artemether-lumefantrine (AL), artesunate plus amodiaquine (AS+AQ), artesunate plus mefloquine (AS+MQ), and artesunate plus sulfadoxine/pyrimethamine (AS+SP).

¹ Artemisinin-based combination therapies

2. May 2001 - May 2011: Increasing Access to Effective Antimalarial Medicines

2.1. Purpose and content of the Memorandum of Understanding

To facilitate a broad and equitable access of the medicine to those in need and to control the development of resistance, on 23 May 2001, WHO signed a unique and pioneering agreement with Novartis Pharma AG - at that time the only manufacturer producing a fixed-dose ACT registered by a stringent drug regulatory authority. The agreement, the so called Memorandum of Understanding, valid for a 10-year period until May 2011, contained the following main aspects:

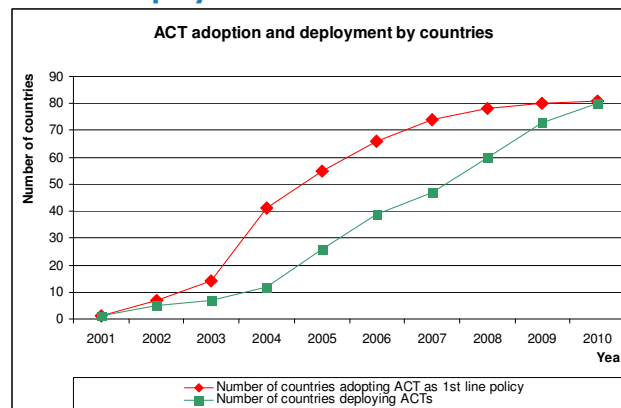
- **Novartis:** To make available artemether/lumefantrine (Coartem®) to WHO at cost price for the supply (on a reimbursable basis) to governments of malaria-endemic developing countries (or organizations working in association with or by permission of such governments) for use in the public sector of these countries.
- **WHO:** To provide Novartis with a 12-months rolling quarterly forecast of expected orders every three months; to convene a Technical Advisory Group of independent experts to advice on the submission requests from countries, in line with national treatment policy and deployment strategies; to request a mutually agreed independent auditor to review the Coartem® price offer at "cost".
- **Both WHO and Novartis:** To collaborate in clinical trials to extend the use of the 6-dose regimen of Coartem® to children of less than 10 kg bodyweight, and to design an appropriate packaging for people with low literacy levels to promote adherence to a full treatment course.

2.2. Impact of the Memorandum of Understanding

2.2.1. Increasing availability of products leading to increasing access to medicines

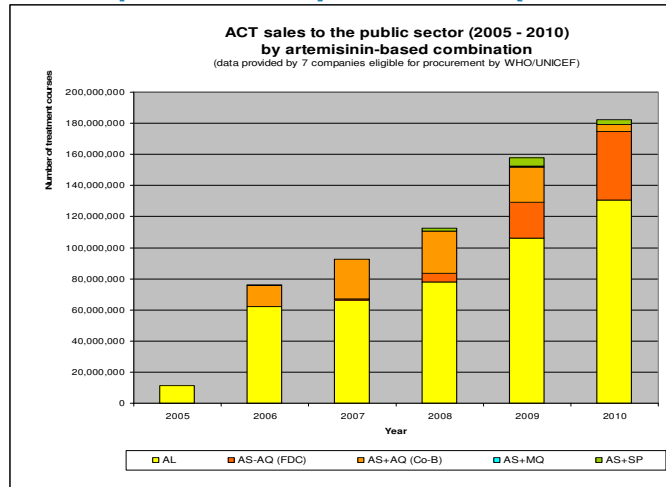
The progressive changes in national medicine policies and the increased deployment of ACTs at country level - generally between 6 to 24 months after the policy adoption (Figure 1) - are reflected by overall annual ACT sales (Figure 2). The number of procured AL treatment courses substantially increased from 11.2 million in 2005 to 77.8 million in 2007, reaching 130.6 million in 2010, with AL accounting for the largest volumes of ACTs procured by the public sector, i. e. 71.6% of the 182,4 million ACT treatment courses² sold by manufacturers of pre-qualified antimalarial medicines for public sector use in 2010.

Figure 1: ACT adoption and deployment



² Sales by 6 of 8 suppliers eligible for WHO/UNICEF procurement.

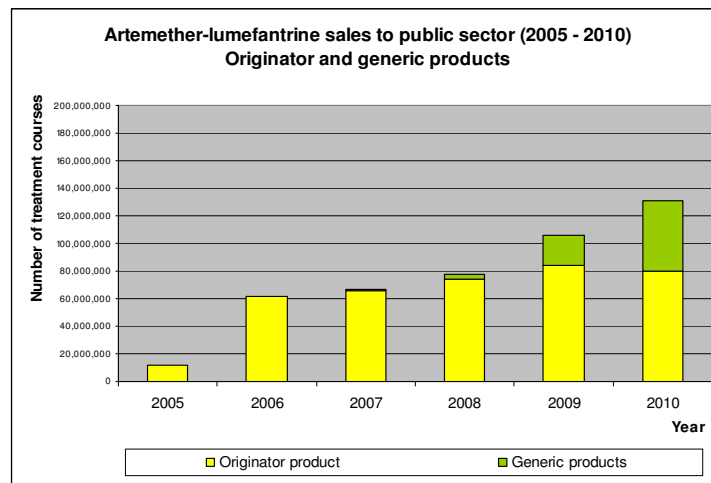
Figure 2: ACT sales to the public sector by combination (2005 - 2010)



A number of additional contributing factors facilitated this rapid scale up of ACT availability:

- **Additional procurement agencies** could benefit from the same price offers set in the MoU between WHO and Novartis, since, over time, Novartis extended the offer to the following agencies: Action Medeor e.V., Catholic Relief Services, Crown Agents, Imres, John Snow Inc (JSI), Malaria Consortium Africa, Medical Export Group, Médecins Sans Frontières (MSF), Medicines for Malaria Venture (MMV), Missionpharma, PAHO, Partnership for Supply Chain Management (PFSCM), Population Service International (PSI), Society for Family Health, Stichting I.D.A., The Mentor Initiative, UNDP, and UNICEF.
- In April 2002, artemether-lumefantrine was also approved for inclusion in the **WHO Model List of Essential Medicines**, a list that is used by most countries to develop a national list of essential medicines of public health relevance for distribution in the public sector.
- **Generic pharmaceutical companies** entered the market after the Novartis product (Coartem®) was prequalified by WHO in April 2004. Three generic Indian companies, Ajanta, Cipla and Ipca, were prequalified by WHO for the production of generic artemether-lumefantrine in December 2008, May 2009 and December 2009, respectively, and were thus also eligible for procurement with international funds (Figure 3).

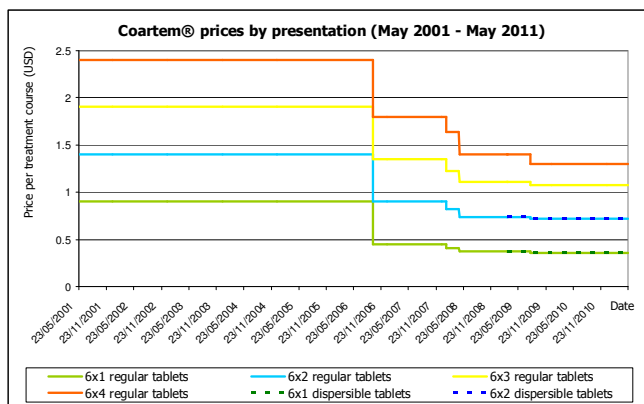
Figure 3: Artemether-lumefantrine sales to public sector (2005 - 2010), Originator and generic products



2.2.2. Decreasing prices

Prices for Coartem® remained stable during the first years of the MoU, ranging between 0.9 - 2.40 USD per treatment course, depending on the age/weight of the patient. The first price reduction was announced by Novartis in September 2006, lowering prices to 0.45 - 1.80 USD per treatment course; the last price reduction was effected in August 2009, with the then-announced prices ranging between 0.36 - 1.30 USD per treatment course still being valid in May 2011. Coartem® dispersible tablets were introduced into the market in March 2009 for both 6x1 tablets and 6x2 tablets presentations at the same price as the regular tablets (6x1 tablets and 6x2 tablets). Figure 4 shows the Coartem® price evolution for the duration of the MoU.

Figure 4: Coartem® prices per treatment course and presentation (May 2001- May 2011)



3. After May 2011: Projections for the artemether-lumefantrine market in the future

3.1. Survey

As per original agreement, the 10-years MoU between WHO and Novartis for the supply of Coartem® at cost price for use in the public sector of malaria endemic countries comes to an end on 22 May 2011. The WHO Global Malaria Programme, as part of WHO's overarching goal to ensure access to quality ACTs at a reasonable price to malaria-endemic countries, undertook a survey on planned AL production capacity by the four WHO-prequalified³ suppliers: Ajanta, Cipla, Ipca and Novartis. Under confidential cover, a questionnaire (Annex 1) was sent to these four companies, and the received data was analysed to develop the most likely supply scenarios for 2011 and 2012 following the termination of the MoU. Companies indicated their total expected production capacity (2011 - 2012) as well as their maximal expected production capacity (2011 - 2013) for AL (both indicated in number of tablets⁴). These data were compared with recent trends in firm orders and the reported information on artemisinin/API⁵ sourcing and inventories for the years 2011 - 2013.

3.2. Development of risk scenarios

The data obtained by the questionnaires (Annex 1) was projected in three possible scenarios. To correct for an over-estimation of the expected production, the assumption was made that only 80% of the indicated total expected production capacity could be reached. The need for this

³ February 2011

⁴ The number of tablets reported by the companies was converted into AL treatment courses, assuming an average treatment course of 16 tablets for the whole period of analysis.

⁵ Active Pharmaceutical Ingredient

correction factor was prompted by a direct comparison of data on recent expected orders for 2010 as reported by the companies at the Artemisinin Conference in Madagascar in October 2010⁶ with the actual sales figures for 2010 as reported to WHO as part of the questionnaire.

The scenarios were developed according to the following criteria:

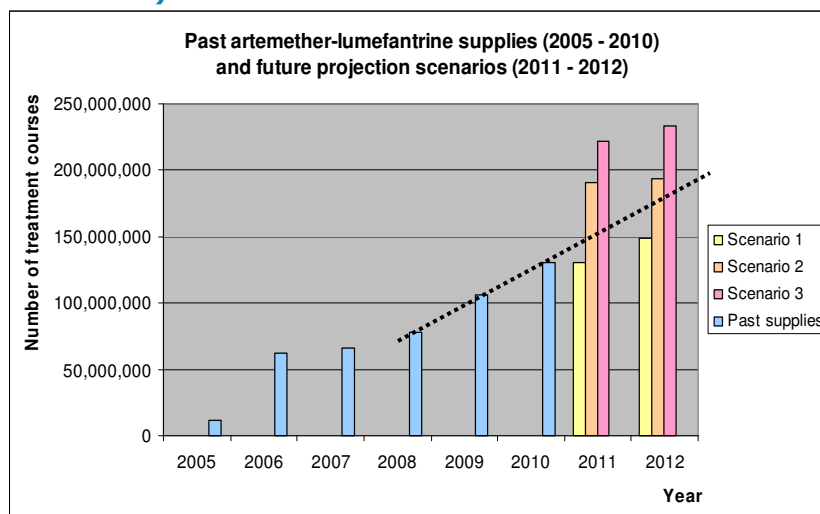
- **Scenario 1:** Two of the four WHO-prequalified companies are producing at 80% levels of the indicated expected production capacity.
- **Scenario 2:** Three of the four WHO-prequalified companies are producing at 80% levels of the indicated expected production capacity.
- **Scenario 3:** All four WHO-prequalified companies are producing at 80% levels of the indicated expected production capacity.

3.3. Interpretation of findings and conclusion

The projected expected AL production for the three risk scenarios (section 3.2) was compared with the expected trend based on the supply in the last three years (Figure 5). In two of the three scenarios (scenarios 2 and 3) the expected AL production matches or exceeds the anticipated increasing demand for supplies as obtained when extrapolating the demand for the years 2008 - 2010. In scenario 1, however, the expected production for 2011 and 2012 will be below this extrapolated anticipated demand.

Both scenario 1 (two inactive companies) and scenario 3 (all four companies producing at 80% levels) seem rather unlikely. On the contrary, scenario 2, providing a cautious expectation of one inactive company, shows that expected production would meet the expected demand for 2011 and 2012. All four companies indicated potential problems in increasing their production due to volatile artemisinin prices, fluctuating availability of artemether or artemisinin raw material, unpredictable sales volumes and unrealistic forecasts. Therefore, due to the dynamic nature of the market and its dependence on agricultural supplies, a reassessment of the supply situation should be undertaken in 2012.

Figure 5: Past artemether-lumefantrine supplies (2005 - 2010) and future projection scenarios (2011 - 2012)



⁶ Artemisinin Conference, Madagascar, October 2010:
http://www.mmv.org/sites/default/files/uploads/docs/artemisinin/2010_Madagascar/ACT_API_Artemisinin_Forecast_and_Supply_A2S2_Monotherapies_and_Substandard_Treatments_Session_Overview.pdf

Annex 1: Questionnaire on artemether-lumefantrine production

Artemether-lumefantrine (20mg/120mg tablets) production						
Contact details		Company name				
		Product name				
		Contact person				
		Telephone				
		e-mail				
Overall production in 2010		Number of treatment courses in 2010				
in number of treatment courses sold and delivered	Public sector	6x1 presentation				
		6x2 presentation				
		6x3 presentation				
		6x4 presentation				
	Private sector	6x1 presentation				
		6x2 presentation				
		6x3 presentation				
		6x4 presentation				
Expected production by year		Number of tablets by quarter				
in number of tablets			Q1	Q2	Q3	Q4
		2011				
		2012				
Maximal production capacity by year		Number of tablets by quarter				
in number of tablets			Q1	Q2	Q3	Q4
2011	in WHO prequalified production facilities based on <i>secured</i> inventory of artemether API*					
	in WHO prequalified production facilities based on <i>anticipated</i> inventory of artemether API*					
2012	in <i>not yet</i> WHO prequalified production facilities based on <i>anticipated</i> inventory of artemether API*					
	in WHO prequalified production facilities based on <i>anticipated</i> inventory of artemether API*					
2013	in <i>not yet</i> WHO prequalified production facilities based on <i>anticipated</i> inventory of artemether API*					
	in WHO prequalified production facilities based on <i>anticipated</i> inventory of artemether API*					
Lead time		Lead time in weeks				
			Minimum	Average	Maximum	
		Lead time (from order reception date to delivery date)				
Reasons for and experiences with long lead times in the past						
Secured API* inventories of artemether and lumefantrine including confirmed contracts with suppliers for 2012 production						
Timelines required to expand production capacity beyond the above mentioned volumes, including time needed for WHO prequalification						
Potential problems to increase production capacity						
Comments						

* API: Active Pharmaceutical Ingredient