

Vaccines for Japanese encephalitis – too early to call for Ixiaro?

LONDON, UK----15th March 2010----ExpertREACT. Recently both the US Advisory Committee on Immunization practices (ACIP) and the UK Joint Committee on Vaccination and Immunization (JCVI) updated their recommendations to include new JE vaccines, specifically Ixiaro® (Novartis/Intercell AG). **VacZine Analytics** discusses these actions in light of Ixiaro's present and expected sales performance.

Japanese encephalitis virus (JEV) is transmitted by *Culex* mosquitoes and principally affects children living in rural Asia and parts of the Western Pacific. Although accurate figures regarding disease burden are unavailable it is commonly estimated that around 35-50,000 people contract JE each year with in the order of 10,000 deaths (US CDC figures). Significantly, many survivors (~30-50% of cases) have severe neurological sequelae heightening further the public health impact of the virus. There is no specific treatment for JE.

Over recent years the focus on vaccines for Japanese encephalitis has increased because new "second generation" cell culture derived vaccines have been developed primarily for use in Western travelers to JE endemic areas. Although the risk of JE for traveler's to Asia is very low, with only 55 travel associated cases between 1973-2008 (1), with increased economic globalization a significant number of Westerners stay for prolonged periods in JE endemic areas where their risk of infection becomes similar to local residents. Importantly these travelers are normally immunologically naïve to JE.

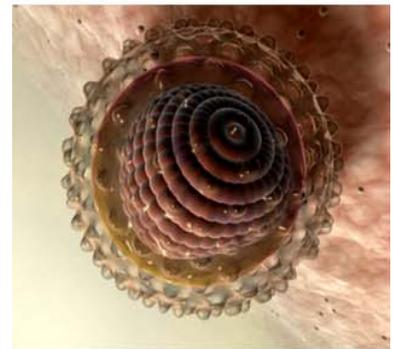
The first new JE vaccine to be licensed is Ixiaro®, which won FDA approval in March 30, 2009 and EU approval in April 02, 2009. The product is marketed by Novartis Vaccines (US/EU/Japan/Korea) being developed by Vienna-based Intercell AG who in-licensed the technology from Vaccgen in April 2003. In Australia, the new JE vaccine is marketed under the tradename JESPECT® and marketed by CSL Ltd. Ixiaro® is a 2 dose vaccine (0 and 28 days) indicated for active immunization in persons 17 years of age or older and is based upon an inactivated attenuated strain of JEV propagated in Vero cells. Previously, the most commonly used JE vaccine used in the West (since 1992) was JE-VAX, a mouse-brain derived vaccine distributed by Sanofi Pasteur up until production ceased by the originator Biken in Japan. Now JE-VAX is reserved for US pediatric use until newer generation vaccines gain approval in younger age groups. In JE endemic countries, locally produced cell and mouse brain derived vaccines are also produced.

Since Ixiaro's launch, industry analysts have closely watched its financial performance not only because the product was a new potential source of alliance revenue for Intercell AG, but also maybe a test of the newly formed Novartis Vaccines marketing capability, especially since its HQ relocation to Boston in the key US market. In the near term, the commercial opportunity for Ixiaro® is based upon vaccinating the estimated 18m yearly travelers to JE endemic regions, the majority of which come from European countries, especially the UK, Germany and Nordic countries. In the US market, stimulating increased demand for Ixiaro® is considered challenging because American travelers are notoriously hard to vaccinate, especially if the risk of disease is low. For JE, it is estimated that only 30,000 doses were distributed annually in the US civilian market (1). In addition JE vaccines are relatively expensive with at Ixiaro® priced ~\$195 per course.

Intercell has stated that it expects peak yearly revenues for Ixiaro® to be around €140-200m for the travel segment (2). Other major sources of business are military use and eventual distribution in endemic countries bringing the total expected value to around €300-400m/yr. For travel, Ixiaro® currently has a virtual monopoly although uptake has initially been slow. For the 9 months ended September 2009, Ixiaro® sold €5.6m (3) and the full year at €7.7m (4). These figures are unsurprisingly since much more work needs to be done to ensure optimum product roll-out and awareness building in many of the key markets. Notably, Intercell is also conducting Phase III trials to gain a pediatric label extension for Ixiaro® and for licensure in India with their partner Biological E. Ixiaro® will face stiff competition in endemic markets from Sanofi Pasteur's IMOJEV® which has been filed in Australia and Thailand.

A key driver to uptake of Ixiaro® in the traveler's segment is the evolution and implementation of official vaccine recommendations. These appear to be moving in a favorable direction for Novartis/Intercell in terms of helping delineate who should be offered Ixiaro®. In June 2009, the US ACIP voted on revised recommendations for the use of JEV vaccines in travelers and laboratory workers and now has published full recommendations/reports as of March 12, 2010 (1). The document, which updates the 1993 recommendations, stipulates that JE vaccines are recommended for travelers who plan to spend a month or longer in endemic areas during the JEV transmission season **OR** if during a short stay, plan to travel to rural areas especially during an outbreak. The vaccine might also be recommended to those travelers's who have an uncertain itinerary which may eventually place them at risk.

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An important observation in the new US ACIP document is reference to a market survey based on 1,691 travelers from the US (5). The survey revealed that JE vaccination rates, and preceding recommendations by health care providers prior to travel were far too low when taking into account the destination and type of trip. This is good news for Novartis/Intercell AG who in order to meet their business objectives must increase vaccination rates from the current estimated 1% to a target 4% in 2020 (2). The US ACIP recommendations now give Novartis ammunition to encourage providers to increasingly offer Ixiaro[®] to US travelers.

Second to the US and Japan, tourism data indicate that UK travelers make up a significant proportion of yearly Western trips to JE endemic regions. Again to mirror the situation in the US, Intercell recently announced that the UK Joint Committee on Vaccination and Immunization (JCVI) recently updated the JE chapter of its Immunization against infectious diseases "Green book" to recommend the use of Ixiaro[®] to UK travelers (6). Ixiaro[®] is recommended alongside Green Cross[®], a 3-dose mouse-brain derived product manufactured by Berna Biotech which reserved for children 1-17 yrs of age but not licensed in the UK (7).

It is a fair assumption that recommendations to travelers will be updated in all major Western countries to reflect the new situation in the US/UK. These changes will facilitate higher uptake of Ixiaro[®] in 2010 with a predicted doubling to trebling of 2009 sales. However, bearing in mind the potential return on marketing investment when compared to Novartis' newly approved Menveo (MenACWY-CRM), and lucrative H1N1 pandemic vaccines, we speculate Intercell AG will need to campaign hard with Novartis management to ensure Ixiaro[®] receives the constant attention it deserves. It is after all a long-term bet.

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References and Notes:

- 1) Japanese Encephalitis Vaccines. Recommendations of the Advisory Committee on Immunization Practices (ACIP). Available at: http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5901a1.htm?s_cid=rr5901a1_e. Accessed March 2010.
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- 6) Intercell AG. Corporate Press Release. March 4th 2010. Available at: http://www.intercell.com/main/forbeginners/news/not-in-menu/news-full/back_to/main/article/joint-committee-on-vaccination-and-immunization-jcvi-in-the-uk-broadens-japanese-encephalitis-immu/. Accessed March 2010.
- 7) Immunization against infectious diseases – 'The Green book'. Chapter 20 – Japanese Encephalitis. UK Department of Health website. Available at: http://www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/@dh/@en/documents/digitalasset/dh_113536.pdf. Accessed March 2010.

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