Dear Dr. Hill,

As requested, here are my comments for the upcoming meeting. I have focused on the pediatric needs. It is interesting that there are 3 artemisin combination treatments for the Committee to consider at this meeting. The potential to include all ACTs on the Essential Medicines List may provide competition to maintain a low price, which would be a public health benefit. This public health benefit should be considered against the public health problem of redundancy in the Essential Medicines List.

Proposed Additions

20 mg Zn supplement formulation

This addition is requested as a cost saving measure under the assumption that 20 mg supplementation to a small infant by mistake (instead of recommended 10 mg) will be safe. No safety data was presented. The only clinical information I could find was a case report from Japan (Sugiura et al 2005 see below) that described developmental delay, anemia and neutropenia due to interference of therapeutic zinc with normal copper metabolism. Without additional information estimating the number of children undertreated with the 10 mg formulation and information about the potential for toxicity if all zinc dosing was switched to 20 mg, it is difficult to provide a rational recommendation to the Committee.

Gatifloxacin:
The safety concern causing the withdrawal from the US market was hyper- and hypo-glycemia. The best public data on the absolute incidence of excess hypoglycemia with Gatifloxacin is 10/1000 adult patient-yrs (Graumlich et al 2005 see below). This risk must be compared with the risk of progressive disease from otherwise untreatable drug-resistant enteric fever including approximately 1% mortality (Reference 7 of submission). For this reason, I support the addition of gatifloxacin for enteric fever in both children and adults.

Artesunate/Amiodaquine
If approved, this would be the second combination artemesin product on the Essential Medicines List. As a pediatrician, I want to focus on the population that suffers the highest mortality from malaria--young children. Since the currently listed artemeter/lumafantrine has a lower limit of dosing of 5 kg and AS/AQ has a lower limit of 4.5 kg, AS/AQ would provide an artemesin product for children between 4.5 and 5 kg (approximately 1 to 3 month infants) who do not currently have coverage. Otherwise, the only advantage of this addition to the list would be to reduce the posology from twice daily to once daily. There is currently no evidence that compliance differs between once and twice daily regimens. The once daily posology of AS/AQ is unlikely to impact the risk of development of resistance from partial compliance. Therefore the application for
AS/AQ brings only marginal public health benefits. It is my hope that if the Committee decides to move to acceptance, then it will be for the benefit of the infants covered by AS/AQ that would not be covered by artemeter/lumafantrine.

Dihydroartemisinin/piperaquin
This artemisin based combination therapy is the 2nd to be considered at this meeting (see above). Similarly to artemeter/lumafantrine, no data on children <5kg was reported. As stated in the support letter from Dr. Schmatz of MMV, the key to this product's value is whether or not manufacturing quality can be maintained. Assuming that Sigma Tau succeeds in manufacturing a reliable GMP product, the advantage of DHA/PPQ would only be as a back-up choice to the existing listed artemesin combination therapy(ies).

Artesunate/pyronaridine
This artemisin based combination therapy is the 3rd to be considered at this meeting (see above). From a pediatric perspective it is unfortunate that the lower weight limit was 5 kg. There appears to be limited data on children under 5 yrs, the group with the highest mortality. The safety data on children under 5 years includes several respiratory complaints which would be worth discussing with the applicant to determine whether there may be a unique toxicity of AS/PY in small children.

From an efficacy perspective, the data on P vivax infection is interesting, but insufficient case numbers make a decision about listing as an Essential Medicine difficult. Currently listed treatments for P vivax are chloroquine, primaquine and Artemeter/lumafantrine. Resistance of P vivax to chloroquine is emerging, but primaquine or AL resistance has not yet been reported. Therefore, there is no public health imperative for adding a new medicine for P vivax.

In summary, AS/PY data indicate that it is effective for P falciparum, but there are safety questions about children’s respiratory symptoms and generally limited data on pediatric exposures. The theoretical advantage of the long half-life of PY that appears to provide some protection against reinfection with P. falciparum (Fig 9 p43) is the only positive unique characteristic offered by AS/PY. This may not be sufficient for listing as an Essential Medicine.

Daranavir
If approved, this would be the 6th protease inhibitor on the essential drug list. As noted by the applicant, darunavir needs to be co-administered with ritonavir, but this is not an application for a combination product. The clinical role for this product is as a component of "salvage" therapy. Though the pharmacokinetics of darunavir would indicate that it may have a use in preventing perinatal infection (Patterson et al 2010 see below), no data supporting that indication have been presented. It is also disappointing that no pediatric data is presented. Finally, the limited number of tablet sizes limit the utility of this medicine.

In conclusion, since the ARTEMIS and TITAN studies indicate that darunavir/ritonavir is superior to lopinavir/ritonavir, darunavir may bring hope for adult patients with multiply resistant virus infection. Such a narrow clinical utility may not be a sufficient public health advantage to be listed as an Essential Medicine.

Etravirine
Though mentionned in the letter from B. Baeten, no data on Etravirine was presented. Looking at virologic data (Clumneck et al 2010 see below), etravirine is an interesting non-nucleoside reverse transcriptase inhibitor and probably has a similar role in salvage therapy as darunavir.

Glucagon
I support the application from Cornell supervised by Dr. Marcus Reidenberg and recognize 2011-02-28
the conflict of interest from a family and institutional perspective.

**Imatinib**

This drug is an enormous scientific advance in cancer therapy. The selectivity of imatinib in the treatment of Ph-chromosome positive tumors is extraordinary. However, the Ph-chromosome positive tumors are quite rare. The new COG data indicate that imatinib may replace the need for resource intensive stem cell transplantation. When sufficient data is available to confirm that imatinib treatment limits the need for resource intensive stem cell transplantation, then the public health benefit in making treatment of Ph-chromosome positive tumors accessible in resource poor countries may warrant the inclusion of imatinib in the Essential Medicines List. At present, imatinib appears to offer too few public health benefits to be included in the Essential Medicines List.

**Midazolam**

The applicants report that midazolam is already on the WHO model formulary for palliative procedures, but I could not find it in the document. Looking at anti-epileptics, midazolam would be the third benzodiazepine on the WHO Model Formulary for Children after diazepam and lorazepam. It offers much faster onset/offset of action making it a much better choice for conscious sedation and for pre-operative sedation than the current benzodiazepines on the Essential Medicines List. Sufficient efficacy and safety data was presented to show that use of midazolam will improve the quality of sedation over currently listed diazepam and lorazepam, thereby providing a public health benefit for this very common medical need. I concur with the recommendation to include midazolam on the Essential Medicines List.

**Miltefosine**

It is very gratifying to see the amount of data accumulated since 2004. This data is compelling evidence for the public health advantages of miltefosine over the currently listed toxic treatments: antimony and amphotericin products. Dr. Saravia’s letter highlights the particular advantages of miltefosine for children. I support the inclusion of miltefosine in the Essential Medicines List.

**Ether**

Reinstatement of ether is being considered due to its low cost and ease of use in the absence of supplemental oxygen. It is heartbreaking to read about resource restrictions that require re-considering ether. This primitive and potentially explosive anesthetic should be relegated to historical descriptions. However, the applicant makes a very practical case that operative mortality might be avoided by re-instating ether pending improvement in anesthetic logistical support (especially the supply of oxygen). It must have been painful for the World Federation of Societies of Anesthesiologists to bring this to our attention and we should honor their commitment to saving lives by approving this request.

**Proposed Deletions**

2011-02-28
Antacids

Both aluminum hydroxide and magnesium hydroxide are included on the Pediatric EML. Since omeprazole and ranitidine are also on the EML, the applicant’s point that antacids are less active in reflux and ulcer disease than other drugs on the EML is accurate. This means that antacids are, at best, second line treatment and at worst redundant. I have no objection to removing antacids from the EML.

Promethazine

The applicants bring an important point to our attention. The applicants present a nice review of clinical trials over time showing advances in anti-emetic therapy (odansetron and follow ons) that have made promethazine obsolete in this indication. Furthermore, sedation medications have also progressed greatly since promethazine was put in “sedation cocktails.” Current sedative medications on the EML are superior in efficacy and safety to promethazine, therefore promethazine should be deleted from the Essential Medicines List.

Oral Salbutamol

The applicants summarize a long discussion that has concluded that beta agonism has no place in the treatment of the wheezy child with viral syndrome. The role of oral salbutamol was primarily in children who could not comply with or could not afford inhaler therapy. Now that data is available that wheezes in viral syndrome do not respond to beta agonism, there is no need to provide an alternate to the inhaler. For care of the asthmatic child, oral beta agonist therapy is of extremely limited utility. Similar to the discussion of ether, the description of resource poor care requiring a second line treatment due to cost constraints must command our attention. Where inhaled steroid and beta agonist treatment is too expensive, oral salbutamol will be better for the asthmatic child than no treatment. Therefore, consider maintaining oral salbutamol on the Pediatric Essential Medicine List, but clearly labeled as second line treatment.

These have been very interesting reviews.

Kind Regards,

Bruce

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Chronic zinc toxicity in an infant who received zinc therapy for atopic dermatitis.

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Abstract

In Japan and many other industrialized countries, zinc is readily available as a nutritional supplement, for cosmetic purposes and for the treatment of atopic dermatitis. The potential risks associated with its use are not, however, fully recognized. As a reciprocal relationship exists between copper and zinc, excessive zinc can produce hypocupraemia, which can cause anaemia and neutropenia. We report on a male infant who presented with anaemia and neutropenia and showed signs of developmental delay after dietary restriction for food allergy and eating difficulties and zinc therapy administered for the treatment of atopic dermatitis at a dose nine times the daily dietary allowance for his age group. After 1 mo of zinc withdrawal, copper and ceruloplasmin concentrations had increased, and the blood cell count had improved, activity was increasing but verbal development remained limited. As development improved after withdrawal of zinc, we cannot rule out a relation between developmental delay and hyperzincæmia and/or hypocupraemia. Conclusion: Caution must be exercised in administering zinc to children during their neurological development.


Hypoglycemia in inpatients after gatifloxacin or levofloxacin therapy: nested case-control study.


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Abstract

STUDY OBJECTIVES: To compare the incidence of hypoglycemic events in patients exposed to gatifloxacin or levofloxacin, and to measure the odds of experiencing a hypoglycemic event after receiving gatifloxacin versus levofloxacin while adjusting for confounders.

DESIGN: Nested case-control study within a historical cohort.

SETTING: A tertiary care, 730-bed, teaching hospital in central Illinois.

PATIENTS: Seven thousand two hundred eighty-seven hospitalized patients who received gatifloxacin or levofloxacin therapy.

MEASUREMENTS AND MAIN RESULTS: A total of 113 patients (case patients) had blood glucose levels below 51 mg/dl; 113 control patients, matched for age and sex, had no hypoglycemia. Matched conditional logistic regression models adjusted the odds of having hypoglycemia for significant covariates. The 12-month incidence of hypoglycemia was 11/1000 patients after levofloxacin administration and 21/1000 patients after gatifloxacin (absolute risk increase 10/1000 patients, 95% confidence interval [CI] 4-16/1000). Renal
failure, sepsis syndrome, and concomitant hypoglycemic drug therapy significantly predicted hypoglycemia. After adjustment for significant predictors, the odds of having hypoglycemia were 2.81 (95% CI 1.02-7.70) times higher after gatifloxacin than levofloxacin therapy.

CONCLUSION: Among inpatients, the incidence of hypoglycemic events is greater after treatment with gatifloxacin than levofloxacin. The odds of experiencing hypoglycemic events are greater with gatifloxacin even after adjusting for other hypoglycemia risk factors, such as concomitant hypoglycemic drugs, renal failure, and sepsis syndrome.


DARUNAVIR, RITONAVIR AND ETRAVIRINE PHARMACOKINETICS IN THE CERVICOVAGINAL FLUID AND BLOOD PLASMA OF HIV-INFECTED WOMEN.

Patterson K, Jennings S, Falcon R, Mrus J, Kashuba A.

University of North Carolina, Chapel Hill, NC, USA; Tibotec Therapeutics, Titusville, NJ, USA.

Abstract

We report darunavir, ritonavir and etravirine pharmacokinetics in cervicovaginal fluid and blood plasma of women from the Gender, Race And Clinical Experience (GRACE) study. Eight women received darunavir/ritonavir 600/100mg twice daily (bid); two also received etravirine 200mg bid. Week 4 paired blood plasma and cervicovaginal fluid samples were collected over 12 hours. Darunavir and etravirine cervicovaginal fluid exposures were higher than blood plasma exposures; ritonavir cervicovaginal fluid exposure was lower than blood plasma exposure. The high exposure of darunavir and etravirine in cervicovaginal fluid warrants further evaluation for use in HIV-1 prevention.


Virological response with fully active etravirine: pooled results from the DUET-1 and DUET-2 trials.


Division of Infectious Diseases, Saint-Pierre University Hospital, Brussels, Belgium.

Abstract

The objective of this subanalysis of the Phase III DUET trials was to examine virological response to an etravirine-containing regimen in patients harbouring virus fully sensitive to etravirine. Full etravirine sensitivity was defined as fold change in 50% effective concentration (FC) ≤3 or weighted genotypic score ≤2. At Week 48 in the etravirine group, 74% of patients with etravirine FC ≤3 and 77% with etravirine genotypic score ≤2 had viral load <50 HIV-1 RNA copies/mL, versus 48% and 46%, respectively, in the placebo group (P < 0.0001). Response rates increased with baseline phenotypic sensitivity score, but were consistently higher with etravirine (56-82%) than placebo (2-72%). Similar observations were made in patients harbouring virus with full etravirine and darunavir sensitivity. Our findings support current recommendations to include three active agents in treatment-experienced patients’ regimens.