Author's response to reviews

Title: Pharmaceutical quality of seven generic Levodopa/Benserazide products compared with original Madopar(R) / Prolopa(R)

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Author's response to reviews: see over
Dear Sirs,

Please find below our point-by-point response to the concerns of the two referees and the changes made in our manuscript „Pharmaceutical quality of seven generic Levodopa/Benserazide products compared with original Madopar® / Prolopa™“.

Reviewer Paolo Calabresi:
- Minor essential revisions
  We corrected several language mistakes, page 8 line 1 (not more than) and line 7 (at least) and last line (cross-scored); page 11 line 1 (excluded); page 12 line 8 (Parkinson’s Disease).

  We wrote consistently numbers in letter in the text and the legends of the figures, e.g. page 2 Results (one or two parameters) and page 9 line 4 (five of the seven).

  We used the term branded products instead of brand; the expression prompt instead of lead to.

  We corrected several misused undefined articles like page 4 line 2 (Typical manifestations) and page 5 line 15 (However, attention is predominantly) and page 8 second last line (The physical characteristics).

  We corrected misspellings page 7 line 18 (weighed).

- Major Compulsory revisions
  Introduction: we added sentences at the end of the Background pointing at the development of complications and stressing at risk factors provoking complications, and added a reference (Go 2011) in order to better understand the consequences of variation of Ldopa bioavailability in the clinical ground, page 5, end of second paragraph (In clinical settings, health professionals are aware that patient response and susceptibility to levodopa vary widely, especially in advanced PD, and that levodopa blood levels correlate with the emergence of many symptoms, including motor manifestations like dyskinesia and “off” periods. Thus, even small variations in levodopa availability and consequently subtle fluctuations in levodopa blood levels can trigger motor complications. Since generic formulations differ from the branded product mainly in their excipients, which may affect absorption and bioavailability, simple bioequivalence cannot suffice to ensure comparable clinical efficacy and safety, especially in PD.)

  Conclusion: we reorganised the conclusion and propose our suggestions, page 11 last paragraph (We recommend considering the substitution of Parkinson’s medication as a medication change, requiring guidance by the patient’s physician. Any generic can be used to initiate first treatment. It will be effective and less expensive than the branded product, but will need a similar process of titration until symptom control is achieved. The challenge for patient, prescribing physician and pharmacist will be to ensure that the same generic formulation is dispensed at each refill. Switching back and forth between brand and generic, or even between generics, is a recipe for problems that may cancel out the savings achieved with the cheaper drug. Ultimately, it is the responsibility of the physician-patient-pharmacist triad to arrive at the best choice for the best patient outcome.)

Reviewer Salvatore Amoroso:
- Do authors have any data concerning pharmacokinetics of the investigated generics: We added some sentences on the worldwide shortage that occurred 2010-11 and its consequences on PK reported by the PD community, page 10 first lines 1ff (In 2010-11 the worldwide shortage of branded Sinemet (carbidopa-levodopa), followed by shortage of its generic formulation (all formulations and all dosages), revealed the distress of the Parkinson community through the testimony of thousands of patients forced to switch to generics. Patients uniformly reported a negative experience and several clinical issues, e.g. slower onset of effect, faster waning of effect, dose adjustment to compensate for the decreased medication effect, symptom exacerbation (e.g. dyskinesia), and side effects such as poorer sleep quality and increased impulsivity. No patient reported a preference for the generic version. Replacement medication was perceived as less effective, probably due to patients receiving differing generics at each renewal, thus getting fluctuations in blood levels with every new product).

We also added comments on two studies on generic levodopa, page 10 lines 14ff (Some small studies suggested that the generic formulation of carbidopa-levodopa given in a single dose to PD patients was bioequivalent to brand Sinemet. However, the same authors report clinical worsening with marked motor fluctuations in a long-term open-label study following conversion to generic carbidopa-levodopa. Approval by the authorities is based on the assumption that demonstrating bioequivalence in pharmacokinetic studies in healthy volunteers suffices to demonstrate similar tolerability and efficacy in patients.)

- Do authors consider this issue a critical point:

Thank you in advance for your review. Kind regards,

/signed
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