Appendix to CMDh position

Divergent positions to CMDh position

Article 31 of Directive 2001/83/EC resulting from pharmacovigilance data

Procedure No: EMEA/H/A-31/1349

Diacerein containing medicinal products

Divergent statement

The undersigned members of CMDh did not agree with the CMDh's position recommending that the marketing authorisations of diacerein containing products should be varied as stated by the CMDh.

The reasons for this divergent opinion were as follows:

Clinical trials and systematic reviews show at best, small beneficial effect of diacerein for treating symptoms of OA of the knee and hip (pain and physical functioning). Structure-modifying effects of cartilage by diacerein in OA have not been demonstrated, so its continuous use cannot be recommended beyond the control of symptoms of OA. Long-term efficacy is not certain and a sparing effect of diacerein on NSAIDs could not be confirmed.

The conclusions derived from most of the reviews are that the strength of evidence for effectiveness outcomes is low to moderate. It was confirmed that symptomatic benefit provided by diacerein in terms of pain reduction is minimal. The small benefit derived in terms of joint space narrowing is of questionable clinical relevance and was observed only for OA of the hip.

Two important safety issues have been identified to potentially impact the benefit-risk balance of diacerein: diarrhoea and hepatic reactions.

Diarrhoea is the most frequent GI effect. Even though MAHs claim most cases are non-severe and transient, some studies suggest that diarrhoea can be chronic (lasting > 4 weeks in up to 25% of diacerein treated patients). Therefore, it is considered that diarrhoea could be a major cause of disability that may led to discontinuation of therapy and serious complications, particularly for elderly patients. The proposed risk minimisation measure for starting the treatment with half the regular daily dose (i.e., 50 mg/day) for the first 2 to 4 weeks is not adequate as half-dose may delay the time onset of diarrhoea and also preclude the efficacy of diacerein. Moreover, insufficient data is available to demonstrate beneficial effects of diacerein with this proposed dose.

OA population includes patients with concomitant regular use of hepatotoxic drugs, such as paracetamol or NSAIDs. As diacerein is an add-on therapy, the simple comparison of adverse events incidence between diacerein and NSAIDs/paracetamol is inadequate. Instead, one has to consider a potential additive or synergistic hepatotoxic effect of these drugs. Although we recognized that diacerein hepatotoxic effect is manifested mainly by mild/moderate increase of liver enzyme with a positive dechallenge, some rare serious cases were described. Additional follow-up measures such as regular monitoring of hepatic enzyme levels during the whole period of treatment could be required for monitoring this safety concern although the feasibility of such measure may be questioned.

Diacerein was proposed as an alternative treatment for patients who are intolerant or have contraindications to first line OA therapies, in particular to NSAIDs. However, diacerein is not indicated in substitution of paracetamol (gold standard for OA symptomatic treatment) or NSAIDs. Moreover, due to its delayed action diacerein is rather use as an add-on therapy, and comparisons should be restricted to the same class of OA treatments, that is, SYSADOAS. If a supplementary therapeutic is

indicated in OA patients, other SYSADOAs alternatives may be safer (e.g. chondroitin sulphate, glucosamine).

Additionally, the risk minimisation activities presented by the MAHs did not provide any reassurance these would be effective regarding the reduction of risks, i.e.:

- the proposed measure to highlight the risk of diacerein-associated hepatotoxicity in the product labelling was not appropriate to reduce the risk of hepatotoxicity to an acceptable level, taking into account the suggested idiosyncratic mechanism of diacerein hepatotoxicity.
- the recommendation of reducing the posology at the start of the treatment to half a dose (50 mg once a day) for the first 2 to 4 weeks, and the recommendation that no laxatives should be used during diacerein treatment, were not appropriate to reduce the risk of severe diarrhoea to an acceptable level, taking into account the lack of data on the impact of a dose reduction with regards to the diminution of incidence and severity of diarrhoea.
- The proposal for limiting the use of diacerein to patients below 65 years to optimise the benefit-risk balance of diacerin is not evidenced by robust data.

The available data suggest that diacerein has a very modest effect on pain reduction, a questionable impact, if any, on function improvement and is a lack of evidence of an NSAID sparing effect. In light of this and given the concerns that remain over the adequacy of the proposed risk minimisation to reduce the risks to an acceptable level, it is considered that the benefit/risk of diacerein containing products is negative.

CMDh member expressing a divergent position:

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Keith McDonald (UK)	23 July 2014	Signature: ……...
Sandra Petraglia (IT)	23 July 2014	Signature: ……...
Susanne Winterscheid (DE)	23 July 2014	Signature: ……...
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