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Committee for Medicinal Products for Human Use (CHMP)

Scientific conclusions and grounds for the variation to the terms of the marketing authorisation(s)

Active substance(s): guanfacine

Procedure No. EMEA/H/C/PSUSA/00010413/201609

Period covered by the PSUR: 18 March 2016 to 17 September 2016

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Scientific conclusions

Taking into account the PRAC Assessment Report on the PSUR(s) for guanfacine, the scientific conclusions of CHMP are as follows:

One serious case of erectile dysfunction, which occurred in the context of a dose upward titration pointing toward a biological gradient or dose response relationship, was reported during the period covered by this Periodic Safety Update Report (PSUR). There is a positive temporal relationship in the development of the Adverse Drug Reaction (ADR) 'erectile dysfunction' and worsening of pruritus and rash pruritic events with a short time to onset (1 day) after the dose increase and these events were resolved after the drug was withdrawn, indicating positive dechallenge. The concomitant medication melatonin is labelled for rash and rash pruritic but not for erectile dysfunction. No other potential confounding factors have been described. The information contained in this single case suggests a positive association between guanfacine and development of erectile dysfunction, which is also supported by the biological plausibility: the nor-adrenergic system is important in controlling male sexual function, from the Central Nervous System through stimulation of those areas regulating penile erection. Male sexual behaviour was suppressed in rats given alpha2-adrenoceptors agonist clonidine by direct injection into the medial preoptic area. There is also evidence for a direct adrenergic regulation of penile veins, the predominant effect occurs through the alpha1-adrenoceptors but there remains the potential involvement of alpha2-adrenoceptors. Stimulation of the alpha2 -adrenoceptors in the cavernosal smooth muscle is known to be involved in erectile dysfunction. The predominant effect occurs through the alpha1-adrenoceptors but there remains the potential involvement of alpha2-adrenoceptors.

Based on the available evidence, the Pharmacovigilance Risk Assessment Committee (PRAC) concluded that erectile dysfunction should be added to section 4.8 of the SmPC under the SOC 'Reproductive system and breast disorders' with a 'not known' frequency with consequential update to section 4 of the Package Leaflet.

Therefore, in view of the data presented in the reviewed PSUR, the PRAC considered that changes to the product information of medicinal products containing guanfacine were warranted.

The CHMP agrees with the scientific conclusions made by the PRAC.

Grounds for the variation to the terms of the marketing authorisation(s)

On the basis of the scientific conclusions for guanfacine the CHMP is of the opinion that the benefit-risk balance of the medicinal product(s) containing guanfacine is unchanged subject to the proposed changes to the product information

The CHMP recommends that the terms of the marketing authorisation(s) should be varied.