Annex II

Scientific conclusions

Scientific conclusions

Haldol Decanoate - an ester of haloperidol and decanoic acid, is a depot antipsychotic belonging to the butyrophenone group. The active substance haloperidol is a potent central dopamine type 2 receptor antagonist, lacking antihistaminergic or anticholinergic activity at recommended doses, and exerts minimal alpha 1 adrenergic activity. After intramuscular injection (IM), Haldol Decanoate is gradually released from muscle tissue and hydrolysed slowly into free haloperidol, which enters the systemic circulation.

Haldol Decanoate has been approved nationally in the EU with many differences in the wording of the summary of product characteristics (SmPC), in the various Member States. Due to the divergent national decisions taken by Member States concerning the authorisation of the above-mentioned product (and its associated names), the European Commission (EC) notified the European Medicines Agency's Secretariat of an official referral under Article 30 of Directive 2001/83/EC in order to resolve the divergences amongst the nationally approved SmPCs and thus to harmonise its divergent SmPCs across the EU.

A critical evaluation of the MAH's proposed harmonised SmPC is discussed below.

Overall summary of the scientific evaluation by the CHMP

Based on the review of all available data and the consultations with the Healthcare Professionals Organisations (HCPOs), the CHMP recommended the following revision and harmonisation of the product information for Haldol Decanoate and associated names.

The final indication agreed for Haldol decanoate is for the maintenance treatment of schizophrenia and schizoaffective disorder in adult patients currently stabilised with oral haloperidol.

The proposal for the posology wording in section 4.2 has been revised with regard to transition from oral haloperidol, continuation of treatment, and supplementation with non-decanoate haloperidol up to the maximum oral dose, in adults and the elderly. Based on clinical trial data, guideline recommendations and expert consultations by the marketing authorisation holder (MAH) and by the HCPOs, a conversion factor of 10 to 15 is supported when switching from oral haloperidol to the long-acting injectable (LAI) Haldol Decanoate. However specific guidance on switching from other antipsychotics has not been proposed due to limited data. Given that the maximum dose of oral haloperidol in the elderly is 5 mg/day and applying the conversion factor of 15, the maximum haloperidol decanoate dose must not be in excess of 75 mg/4wk in the elderly unless elderly patients have already received higher haloperidol (oral or decanoate) doses for long-standing schizophrenia with acceptable tolerability. In patients with hepatic impairment, it is recommended to halve the initial dose, since haloperidol is extensively metabolised in the liver. Also patients with severe renal impairment may require a lower initial dose, with subsequent adjustments.

As Haldol Decanoate is an injectable long-acting depot formulation recommended to be used every 4 weeks, in order to avoid medication errors in which either haloperidol injectable or haloperidol decanoate are administered in error, the MAH has committed to conduct further post-marketing safety analysis after completion of the Art 30 referral, while assessing the need for changing the name of the medicinal product thereafter.

The contraindications in section 4.3 were also amended to include the wording related to the contraindication of cardiotoxic risk of haloperidol. Contraindications relating to children less than 3 years of age and breastfeeding women were not included due to the lack of adequate data to support such contraindications. The list of examples of contraindicated combinations considered essential for

the prescriber to be informed of the risk of an additive QT prolonging effect of two or more QT prolonging antipsychotics, was moved to section 4.4.

In section 4.4; Special warnings and precautions for use, the following changes have been included:–The information under the subheading extrapyramidal symptoms was further elaborated to include the symptoms and time to onset of acute dystonia and akathisia. Furthermore, observational studies have consistently reported an increased mortality in elderly haloperidol users - the highest mortality risk with haloperidol was in the first 30 days and persists for at least 6 months. Caution is also recommended when using Haldol in patients with pre-existing hyperprolactinaemia and in patients with possible prolactin-dependent tumours

As CYP3A4 and, to a lesser extent, CYP2D6 are involved in the metabolism of haloperidol, the potential increase in haloperidol plasma concentrations when a CYP3A4 and/or CYP2D6 inhibitor is coadministered may range between 20 to 40%, although in some cases, increases of up to 100% have been reported, and has been added in section 4.5 Interaction with other medicinal products and other forms of interaction.

Section 4.6 has been harmonised and the information presented under the separate subheadings of Pregnancy, Lactation and Fertility in compliance with the SmPC guideline.

Minor changes were included in the remaining sections of the SmPC. The changes to the SmPC, when relevant for the user, have also been reflected in the PL and agreed by the CHMP.

An HCPO consultation was carried out during this procedure. The questions to the HCPOs mainly pertained to the dosing recommendations in clinical practice (section 4.2) as well as the contraindication for haloperidol decanoate due to central nervous system depression, and whether it was possible to define the severity/degree of central nervous system depression due to alcohol or other depressant medicinal products, and whether there specific cases where the use of Haldol Decanoate should be contraindicated..

The discussion and conclusions reached by the HCPOs were taken into account in the final deliberations of the CHMP as mentioned above. The final agreed indication can be found above.

Grounds for the CHMP opinion

Whereas

- The Committee considered the referral under Article 30 of Directive 2001/83/EC for Haldol Decanoate and associated names;
- The Committee considered the divergences identified in the notification for Haldol Decanoate and associated names, as well as the remaining sections of the product information;
- The Committee reviewed the totality of the data submitted by the MAH in support of the proposed harmonisation of the product information. In addition, the committee considered the advice of the consulted Healthcare Professionals Organisations.
- The Committee agreed on a harmonised product information for Haldol Decanoate and associated names.

In view of the above, the Committee concluded that the benefit-risk balance of Haldol Decanoate and associated names remains favourable, subject to the agreed amendments to the product information

The Committee as a consequence, recommends the variation to the terms of the marketing authorisations for which the product information is set out in Annex III for Haldol Decanoate and associated names (see Annex I).