Annex II

Scientific conclusions

Scientific conclusions

Haldol, which contains the active substance haloperidol, is an antipsychotic belonging to the butyrophenone group. It is a potent central dopamine type 2 receptor antagonist, and at recommended dosages, has no antihistaminergic or anticholinergic activity and minimal alpha 1 adrenergic activity.

Haldol has been approved nationally in the European Union (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, the consultations with the Healthcare Professionals Organisations (HCPOs) and Scientific Advisory Group (SAG) Psychiatry, the CHMP recommended the following revisions to harmonise the product information for Haldol oral and injectable formulations.

The revised indications are:

For the oral formulations:

- Treatment of schizophrenia and schizoaffective disorder.
- Acute treatment of delirium when non-pharmacological treatments have failed.
- Treatment of moderate to severe manic episodes associated with bipolar I disorder.
- Treatment of acute psychomotor agitation associated with psychotic disorder or manic episodes of bipolar I disorder.
- Treatment of persistent aggression and psychotic symptoms in patients with moderate to severe Alzheimer's dementia and vascular dementia when non-pharmacological treatments have failed and when there is a risk of harm to self or others.
- Treatment of tic disorders, including Tourette's syndrome, in patients with severe impairment after educational, psychological and other pharmacological treatments have failed.
- Treatment of mild to moderate chorea in Huntington's disease, when other medicinal products are ineffective or not tolerated.

For the injectable formulations:

- Rapid control of severe acute psychomotor agitation associated with psychotic disorder or manic episodes of bipolar I disorder when oral therapy is not appropriate.
- Acute treatment of delirium when non-pharmacological treatments have failed.
- Treatment of mild to moderate chorea in Huntington's disease, when other medicinal products are ineffective or not tolerated, and oral therapy is not appropriate.
- Single or combination prophylaxis in patients at moderate to high risk of postoperative nausea and vomiting, when other medicinal products are ineffective or not tolerated.

- Combination treatment of postoperative nausea and vomiting when other medicinal products are ineffective or not tolerated.

Paediatric indications were agreed only for the oral formulations for the treatment of:

- Schizophrenia in adolescents aged 13 to 17 years when other pharmacological treatments have failed or are not tolerated.
- Persistent, severe aggression in children and adolescents aged 6 to 17 years with autism or pervasive developmental disorders, when other treatments have failed or are not tolerated.
- Tic disorders, including Tourette's syndrome, in children and adolescents aged 10 to 17 years with severe impairment after educational, psychological and other pharmacological treatments have failed.

As regards the posology, section 4.2 of the SmPC, the initial and maximum doses were clarified and listed for each indication, for all patient populations - adult, elderly and paediatric. It was agreed that the maximum dose in elderly patients should be 5 mg/day, while higher doses should only be considered in patients who have tolerated higher doses and after reassessment of the patient's individual benefit-risk profile. 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.

Section 4.3 was 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 risk of a rapid switch to depression in patient populations with bipolar disorder was added under a separate subheading, also advising close supervision of patients and in particular those at high risk. 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.

Angioedema was added to section 4.8 Undesirable effects and additional information on the site of action of injectable haloperidol in the treatment and prophylaxis of nausea and vomiting has been included in section 5.1 Pharmacodynamic properties.

In section 5.2 Pharmacokinetic properties, a statement that back–conversion to haloperidol cannot be fully excluded has been included although it is not possible to quantitate the role of back-oxidation of

reduced haloperidol to haloperidol on haloperidol half-life, clearance and activity. It is advised that measurement of haloperidol concentrations may be considered in individual cases.

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 endorsed by the CHMP.

A SAG and HCPOs consultations were carried out during this procedure at the request of the CHMP.

The questions to the HCPOs mainly pertained to the clinical value of the indications (section 4.1) and dosing recommendations in clinical practice (section 4.2), as well as the contraindication for haloperidol 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 haloperidol should be contraindicated. The SAG Psychiatry was consulted on the clinical value of the following adult and paediatric indications (section 4.1) and also on dosing recommendations in clinical practice (section 4.2):

- Treatment of schizophrenia in paediatric population
- Agitation, aggression and psychotic symptoms associated with dementia
- Treatment of acute alcohol intoxication
- Tic disorders including Tourette's syndrome
- Symptoms of persistent aggression in children with autism or pervasive developmental disorders

The discussion and conclusions reached by the HCPOs and SAG Psychiatry were taken into account in the evaluation by the CHMP, and are reflected in the relevant sections above.

Grounds for the CHMP opinion

Whereas

- The Committee considered the referral under Article 30 of Directive 2001/83/EC for Haldol and associated names;
- The Committee considered the divergences identified in the notification for Haldol 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 (HCPOs) and SAG Psychiatry.
- The Committee agreed on a harmonised product information for Haldol and associated names.

In view of the above, the Committee concluded that the benefit-risk balance of Haldol 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 and associated names (see Annex I).