EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Referral under Article 30 of Directive 2001/83/EC

Haldol Decanoate and associated names

Active substance: haloperidol decanoate

Procedure number: EMEA/H/A-30/1405

Note:

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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1. Background information

Haldol Decanoate and associated names was included in the list of products for summary of product characteristics (SmPC) harmonisation, drawn up by the CMDh, in accordance with Article 30(2) of Directive 2001/83/EC.

Due to the divergent national decisions taken by Member States concerning the authorisation of the above-mentioned product, the European Commission (EC) therefore notified the European Medicines Agency on 18 June 2014 of a referral under Article 30 of Directive 2001/83/EC for Haldol Decanoate and associated names, in order to resolve divergences amongst the nationally authorised product information and thus harmonise the product information across the EU.

The scope of this procedure concerns Haldol Decanoate injectable solution 50mg/ml, 100mg/ml and 150mg/3ml.

2. Scientific discussion during the referral procedure

2.1. Introduction

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.

The approved pharmaceutical form of Haldol Decanoate in the European Union (EU) is the solution for injection (50mg/ml, 100 mg/ml and 150mg/3ml). 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.

Haldol was included in the list of products for the harmonisation of the summary of product characteristics (SmPC), drawn up by the Co-ordination Group for Mutual Recognition and Decentralised Procedures – human (CMDh), in accordance with Article 30(2) of Directive 2001/83/EC. 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.

2.2. Critical Evaluation

Summary of product characteristics (SmPC)

<u>Section 4.1 – Therapeutic Indications</u>

Maintenance treatment of Schizophrenia

Haloperidol Decanoate is approved for the indication '*Maintenance treatment of schizophrenia'* in 10 European Union (EU)/European Economic Area (EEA) Member States.

In support of this indication, the marketing authorisation holder (MAH) presented study data from 11 internal trials (mostly uncontrolled), one Cochrane review on haloperidol decanoate for schizophrenia, and two published randomised double-blind studies.

It is noted that almost all studies were not blinded and a placebo control was not included. Patients were mostly diagnosed with schizophrenia; however, few patients with other psychiatric diagnoses were also included. The duration of the studies was mainly 24 weeks, which is in accordance with the maintenance treatment claim. Despite the limitations in study design in most of the studies presented, it could be unequivocally shown that haloperidol decanoate is effective in the maintenance treatment of schizophrenia.

The Cochrane review cited also demonstrated efficacy compared to placebo. Furthermore, no discernible differences were found between haloperidol depot and the oral formulations, and between haloperidol depot and other depot neuroleptics.

Following consideration of additional reviews presented by the MAH, it was noted that a few patients with a diagnosis varying from schizophrenia had also been included in the studies. The majority of the subjects treated with haloperidol decanoate for these indications other than schizophrenia, suffered from schizoaffective disorders. Therefore the CHMP agreed to include schizoaffective disorders in the indication.

There are no data to support the restriction of the indication for haloperidol decanoate in patients for whom oral treatment is not feasible. In clinical studies, patients were mostly reported to have received prior treatment with orally administered haloperidol before converting to haloperidol decanoate and only limited data are available in regard to conversion from other oral antipsychotics to haloperidol decanoate. Therefore the indication has been refined as follows:

'HALDOL Decanoate is indicated for the maintenance treatment of schizophrenia and schizoaffective disorder in adult patients currently stabilised with oral haloperidol (see section 5.1)'.

The final agreed wording for this section of the SmPC can be found in Annex III of the CHMP opinion.

Section 4.2 - Posology and method of administration

Posology

Haloperidol Decanoate should only be indicated in patients, who have already been treated with oral haloperidol (or oral neuroleptics) and for whom efficacy and safety of oral therapy has been established. As a consequence, conversion of oral antipsychotic treatment should therefore be commenced based on the daily dose of the oral treatment. Based on the totality of available data in particular clinical trial data, and having noted the relevant guideline recommendations and expert consultations by the MAH and by Healthcare Professional Organisations (HCPOs), a conversion factor of 10 to 15 is supported when switching from oral haloperidol to the long-acting injectable (LAI) Haldol Decanoate. Specific guidance on switching from other antipsychotics has not been proposed due to limited data.

The CHMP's proposal not to mention initial haloperidol decanoate doses was also supported by the HCPOs, and a dose of 300 mg for adults was agreed to be the maximum 4-week dose. In the elderly, maximum haloperidol decanoate dose was finally agreed to be 75 mg/4 week, with higher doses only to be considered in patients who have tolerated higher doses and after re-assessment of the patient's individual benefit-risk profile. As a gradual dose increase recommendation of 50 mg has not been sufficiently addressed by clinical data, a more general advice to not exceed 50 mg as a titration step has been introduced.

Based on literature data, the possibility of oral supplementation with haloperidol (if clinically indicated) has also been included and combined total dose of haloperidol from both formulations (decanoate and oral) is restricted to the maximum dose indicated for oral haloperidol.

Overall, the posology wording in regard to transition, continuation and supplementation of treatment, as proposed by the CHMP was agreed by the MAH.

There are no data to support the advice regarding the reduction of the dose after long term treatment therefore this wording is not included in the proposed SmPC.

Method of administration

Haloperidol Decanoate is for intramuscular use only to be administered as a deep intramuscular injection in the gluteal region. Haloperidol Decanoate must not be administered intravenously.

Paediatric population

Haloperidol Decanoate is not intended for use in children.

Elderly population

As age is a major factor that contributes to neuroleptic dosing, a 50% dose reduction in the elderly has been observed, as they are especially sensitive to adverse effects of antipsychotic drugs (sedation, extrapyramidal Symptoms (EPS), tardive dyskinesia, anticholinergic adverse events and orthostatic dysfunction). The initial doses of 12.5 to 25 mg/4 weeks in the elderly were justified by the MAH and agreed by the CHMP. Up-titration is recommended only if required (based on individual patient response) until an optimal therapeutic effect is obtained.

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.

Renal impairment

No dose adjustment has been recommended in patients with renal impairment. However the influence of renal impairment on the pharmacokinetics of haloperidol or reduced haloperidol has not been evaluated and therefore caution is advised. Therefore the wording in this subsection was revised to include the information that patients with severe renal impairment may require lower starting dose with dose adjustments at smaller increments and at longer intervals.

Hepatic impairment

No studies were retrieved examining the pharmacokinetics of haloperidol decanoate in patients with hepatic impairment. Taking into account the extensive biotransformation of haloperidol in the liver and the propensity of being a moderately extractable drug with moderate hepatic extraction ratio, the MAH agreed to include a cautious wording for patients with hepatic impairment i.e half of the initial dose and dose adjustments with small increments and longer intervals.

The final agreed wording for this section of the SmPC can be found in Annex III of the CHMP opinion.

Section 4.3 – Contraindications

Haloperidol decanoate has been contraindicated in patients with Parkinson's disease, dementia with Lewy bodies, and comatose state, progressive supranuclear palsy and CNS depression due to alcohol or other depressant drug. The severity/degree of central nervous system depression due to alcohol or other depressant medicinal products was considered by CHMP and also by the HCPOs. However the severity/degree of central nervous system depression when haloperidol should be contraindicated has

not been defined, as there is no adequately supported scale/technique that could be used in order to measure CNS depression and predict hypoxic events. However, as CNS depression is not only caused by alcohol or depressant medicinal products, the MAH has amended the contraindication in order to address all possible causes of CNS depression, to read: *Central nervous system (CNS) depression.*

The MAH also agreed to include the wording related to the contraindication of cardiotoxic risk of haloperidol, (i.e inclusion of: *known QTc interval prolongation or congenital long QT syndrome, recent acute myocardial infarction, uncompensated heart failure, history of ventricular arrhythmia or torsades de pointes, uncorrected hypokalaemia, concomitant treatment with medicinal products that prolong the QT interval (see section 4.5*).

As there is a lack of data to support contraindications in case of malignant neuroleptic syndrome (NMS), depression and the use of haloperidol with anticoagulant therapy, these have not been included in this section.

Contraindications relating to breastfeeding women were not included due to the lack of adequate data to support such contraindications.

The final agreed wording for this section of the SmPC can be found in Annex III of the CHMP opinion.

Section 4.4 - Special warnings and precautions for use

Only the issues that were discussed are summarised below.

Increased mortality in elderly people with dementia

Despite limitations, observational studies using various analytic methods and results have consistently shown an increased mortality in older haloperidol users. These studies also showed that the mortality risk with haloperidol was highest in the first 30 days and persists for at least 6 months. The extent to which this association is attributable to the antipsychotic medicinal product, as opposed to being confounded by patients' characteristics/clinical status has not yet been elucidated. These findings have been reflected in this subsection of the SmPC.

Cardiovascular effects

Caution is advised for patients taking CYP2D6 and CYP3A4 inhibitors who are at higher risk for developing adverse reactions especially if they also have a pharmacogenetic predisposition. Baseline ECG is recommended prior to treatment in all patients, especially in the elderly and patients with a positive personal or family history of cardiac disease or abnormal findings on cardiac clinical examination.

During therapy, the need for ECG monitoring (e.g. at dose escalation) should be assessed on an individual basis and the dose should be reduced if QT is prolonged, or haloperidol should be discontinued if the QTc exceeds 500 ms.

A recommendation on electrolyte monitoring at baseline and also periodic measurements has been included.

Cerebrovascular events

The risk of stroke for the whole class of butyrophenones instead of solely for haloperidol has been included.

Neuroleptic malignant syndrome

The symptomatology of neuroleptic malignant syndrome (NMS) was further elaborated to include elevated serum creatinine phosphokinase levels.

Tardive dyskinesia

The need for discontinuation when the signs and symptoms of tardive dyskinesia appear has been included.

Extrapyramidal symptoms

The use of haloperidol has been associated with the development of extrapyramidal symptoms such as akathisia, characterised by a subjectively unpleasant or distressing restlessness and need to move often accompanied by an inability to sit or stand still. Additional information on akathisia has been added to include the symptoms that may develop within the first few weeks of treatment and a precautionary statement to avoid increasing the dose in such cases.

Information on the symptoms and time to onset of acute dystonia and the need to stop or reduce the dose if necessary has also been included.

Hepatobiliary concerns

Due to the extensive biotransformation of haloperidol in the liver and the propensity of being a moderately extractable drug with moderate hepatic extraction ratio, the MAH agreed to include a cautious wording for patients with hepatic impairment (half of the initial dose for the injectable formulation and dose adjustments for the oral formulation).

Endocrine system concerns

Although no clear association with the administration of antipsychotics and human breast tumours has been demonstrated in clinical and epidemiological studies, the prescribing physician is alerted that Haldol Decanoate must be used with caution in patients with pre-existing hyperprolactinaemia and in patients with possible prolactin-dependent tumours.

Patients with depression

As with all antipsychotic agents, Haldol Decanoate should not be used alone where depression is predominant.

Bone Mineral density / Osteoporosis

Although hyperprolactinemia, a well-known adverse reaction of haloperidol, might lead to a decrease of bone mineral density and osteoporosis, it is not an independent risk factor for osteoporosis in schizophrenic patients. Based on the submitted data, it was not considered necessary to include the preferred terms (PTs) decreased bone mineral density and osteoporosis in sections 4.4 and 4.8 of the SmPC.

The wording on concomitant administration of antipsychotics was moved from section 4.4 to section 4.5.

The final agreed wording for this section of the SmPC can be found in Annex III of the CHMP opinion.

Section 4.5- Interaction with other medicinal products and other forms of interaction

No specific issues were highlighted regarding this section. However there is a lack of harmony across the Member States, and only the issues that were discussed are summarised below.

In the subsection 'Cardiovascular effects', the addition of a list of examples of contraindicated combinations was considered essential for the prescriber to be informed of the risk of an additive QT prolonging effect of two or more QT prolonging antipsychotics.

The expected increase in haloperidol exposure from concomitant treatment with potent inhibitors of CYP2D6 and/or CYP3A4 has been included. Data are not consistent across studies and increases in

haloperidol concentration ranged between 20% and 40% when a CYP3A4 and/or CYP2D6 inhibitor was coadministered (although mean increases of up to 100% have also been reported). The MAH agreed to the proposal of the CHMP to include more examples of strong CYP2D6 and CYP3A4 inhibitors that have the potential to increase haloperidol plasma concentrations.

Co-administration of medicinal products that decrease haloperidol plasma concentrations such as inducers of CYP3A4 has also been included with examples, although the list is not exhaustive.

Other effects of haloperidol such as its ability to antagonise the action of adrenaline and other sympathomimetic medicinal products (e.g. stimulants like amphetamines) and levodopa and other dopamine agonists has also been included.

The final agreed wording for this section of the SmPC can be found in Annex III of the CHMP opinion.

Section 4.6 – Fertility, pregnancy and lactation

The proposed harmonised SmPC presents the information under the separate subheadings of Pregnancy, Lactation and Fertility in compliance with the SmPC guideline.

Pregnancy

A more cautious wording on avoiding intake of haloperidol during pregnancy was included under this subsection based on the insufficient data available to exclude a teratogenic potential of haloperidol. Therefore as a precautionary measure, it is recommended to avoid the use of Haldol during pregnancy, as newborn infants exposed to antipsychotics (including haloperidol) during the third trimester of pregnancy are at risk of adverse reactions including extrapyramidal and/or withdrawal symptoms, which may vary in severity and duration following delivery.

Breastfeeding

Haloperidol is excreted in breast milk, and it has been shown that small amounts of haloperidol have been detected in plasma and urine of breast-fed newborns of mothers treated with haloperidol. A decision whether to discontinue breastfeeding or to discontinue Haldol therapy must be made taking into account the benefit of breastfeeding for the child and the benefit of therapy for the woman.

Fertility

Haloperidol can affect gonadal function by suppressing the production of gonadal hormone/gonadotropins via increased levels of prolactin. Further research has not been conducted to evaluate fertility in humans, therefore it was considered acceptable to include a general wording supporting the correlation of high prolactin levels caused by haloperidol and subsequent suppression of hypothalamic and pituitary hormones resulting in altered gonadal steroidogenesis in women and men.

The final agreed wording for this section of the SmPC can be found in Annex III of the CHMP opinion.

Section 4.7 - Effects on ability to drive and use machines

Placebo and active-comparator controlled studies showed that a majority but not all of the patients had some impairment of driving ability. Therefore cautionary wording has been included that patients are advised not to drive or operate machinery during treatment, until their susceptibility is known, since haloperidol has a variable impact on reaction time and motor skills between inter subjects as well as dose variability. Potentiation of impairment of alertness or sedation by alcohol has also been mentioned.

The final agreed wording for this section of the SmPC can be found in Annex III of the CHMP opinion.

Section 4.8 - Undesirable effects

Section 4.8 is based on all available data. A single table has been proposed that includes ADRs identified in clinical trials with haloperidol and haloperidol decanoate including postmarketing experience.

The adverse reactions angioedema and rhabdomyolysis were discussed and added to the list of adverse reactions.

The final agreed wording for this section of the SmPC can be found in Annex III of the CHMP opinion.

Section 4.9 – Overdose

The structure and content of section 4.9 is in line with the SmPC guideline. This section begins by stating that overdose is less likely to occur with parenteral than with oral medication. The remaining details are based on oral haloperidol.

The signs and symptoms of haloperidol overdose and treatment have been listed adequately in this section. Signs and symptoms of anticholinergic reactions following overdose of haloperidol have not been included due to the lack of evidence. There is no specific antidote in cases of overdose, and recommendations for the supportive treatment of severe arrhythmias, extrapyramidal reactions and hypotension/circulatory collapse have been included. Dialysis is not recommended in the treatment of overdose because it removes only very small amounts of haloperidol.

Regarding doses that may lead to intoxication in children and adults, data on the actual amount of ingested drugs are generally lacking and it is difficult to trace back serum concentrations on potential doses due to a large variability. Therefore information on doses has not been included in this section.

Taking into account the extended duration of action of Haldol Decanoate, the treatment of severe extrapyramidal reactions has been included.

The final agreed wording for this section of the SmPC can be found in Annex III of the CHMP opinion.

Section 5.1 - Pharmacodynamic properties

While haloperidol is capable of binding to receptors other than the D2 dopamine and α1 adrenergic receptors, this only happens at concentrations significantly higher than those that would be prescribed in clinical practice. Therefore the SmPC wording describes the mechanism of action of haloperidol as a potent central dopamine type 2 receptor antagonist, while having low alpha-1 antiadrenergic activity and no antihistaminergic or anticholinergic activity at recommended doses.

The wording has been clarified that most of the patients in the clinical studies presented were reported to have received prior treatment with orally administered haloperidol before converting to haloperidol decanoate, although some had previously been treated with other antipsychotics.

The wording was also refined to reflect that haloperidol suppresses the positive symptoms such as hallucinations and delusions that are the result of overactivity in the mesolimbic dopamine pathway.

Clarity on the anatomical localisation for the site of action (on lactotropes in the anterior pituitary) of the antidopaminergic effects of haloperidol causing hyperprolactinemia has been included.

Although anhedonia is a generally recognized symptom of schizophrenia, the MAH was unable to retrieve any evidence that haloperidol causes or aggravates anhedonia, and therefore no additional wording to the SmPC was suggested.

The final agreed wording for this section of the SmPC can be found in Annex III of the CHMP opinion.

Section 5.2 - Pharmacokinetic properties

The pharmacological effects of haloperidol decanoate are those of haloperidol, which is released by bioconversion.

Absorption

After intramuscular injection with haloperidol decanoate, concentrations of free haloperidol generally peak in the first week after the injection, and gradually decrease towards week 4. Steady-state concentrations of haloperidol after intramuscular injection with haloperidol decanoate strongly correlate with dose and are reached within 2-4 months.

Distribution

A high inter-individual variability has been found for plasma protein binding as well as volume of distribution. Haloperidol is rapidly distributed to various tissues and organs, as indicated by the large volume of distribution (mean steady state values 8 to 21 L/kg after intravenous dosing). Concentrations in the cerebrospinal fluid (CSF) were about 10% of serum concentrations. Rowell (1981)[1] found the percentage of free haloperidol at 12.5% (±4.3%). The wording proposed by the MAH referring to the pertinent literature for distribution data was considered to be acceptable.

Biotransformation

Haloperidol is metabolized by several routes. The major pathways are glucuronidation and ketone reduction. The greatest proportion of the intrinsic hepatic clearance of haloperidol is by glucuronidation, followed by reduction of haloperidol to reduced haloperidol. The cytochrome (CYP) P450 enzyme system is involved in the reduction of haloperidol to reduced haloperidol particularly by CYP3A4 and, to a lesser extent, CYP2D6 (the exact role and importance of CYP2D6 in the metabolism of haloperidol or the back-oxidation of reduced haloperidol to haloperidol remains unclear).

The reduction pathway accounts approximately for 23% of the biotransformation. Since reduced haloperidol has 10 to 25% activity of haloperidol, reduced haloperidol may contribute to the overall pharmacological activity of haloperidol through back-oxidation. A statement that back–conversion to haloperidol cannot be fully excluded has been included although it is not possible to quantify the role of back-oxidation of reduced haloperidol to haloperidol on haloperidol half-life, clearance and activity.

Elimination

After intramuscular injection of haloperidol decanoate, elimination half-life was found to be 3 weeks (Reyntjens 1982[2] and Chang 1993[3]). Around 21% of the dose was recovered in the faeces and 33% in urine after intravenous haloperidol administration. This has been adequately included in the harmonised SmPC.

The MAH's proposed wording for this sub-section derived from literature for data on haloperidol decanoate elimination was considered to be acceptable after some revision.

Linearity / non-linearity

There is a linear relationship between single-dose and steady-state pharmacokinetics. Studies have been provided to support the relevant wording in the harmonised SmPC.

[1] Rowell FJ, Hui SM, Fairbairn AF, Eccleston D. Total and free serum haloperidol levels in schizophrenic patients and the effect of age thioridazine and fatty acid on haloperiodol-serum protein binding in vitro. Br J Clin Pharmacol. 1981;11(4):377-382.
[2] Reyntjens AJ, Heykants JJ, Woestenborghs RJ, Gelders YG, Aerts TJ. Pharmacokinetics of haloperidol decanoate: a 2-year follow-up. Int Pharmacopsychiat. 1982;17:238-246.
[3] Chang WH, Lin SK, Juang DJ, et al. Prolonged haloperidol and reduced haloperidol plasma concentrations after decanoate withdrawal. Schizophr Res. 1993;9(1):35-40.

Special populations

Elderly

Pharmacokinetic investigations found higher serum concentrations of haloperidol in the elderly compared to younger adult subjects. Studies show that clearance was found to be lower in the elderly patients and elimination half-life longer than in the younger adult patients (Kelly et al.[4]). In a study evaluating plasma concentrations of haloperidol and reduced haloperidol in elderly and adult patients (Chang 1996[5]), the metabolic ratios of reduced haloperidol to haloperidol were about twice as high in the elderly vs. the adult patients. Dose adjustment has been recommended in elderly patients with a cross-reference to section 4.2.

Renal impairment

Urinary excretion accounts for about one third of elimination of an administered haloperidol dose and less than 3% is excreted unchanged in the urine. Even though impairment of renal function is not expected to affect haloperidol elimination to a clinically relevant extent, in the absence of definitive data, caution is advised in patients with renal impairment. Caution is especially advised for those patients with severe impairment, due to the long half-life of haloperidol and its reduced metabolite (reduced haloperidol has 10 to 25% activity of haloperidol), and the possibility of accumulation. The revised wording proposed by the MAH referring to the special population with renal impairment was considered to be acceptable with a cross reference to section 4.2.

Hepatic impairment

Studies in patients with hepatic impairment are lacking and therefore information retrieved from pharmacokinetic data with haloperidol was taken into consideration. Due to the extensive biotransformation of haloperidol in the liver and the propensity of being a moderately extractable drug with moderate hepatic extraction ratio, the MAH agreed to include dose adjustment and caution for patients with hepatic impairment as mentioned in section 4.2.

Pharmacokinetic/pharmacodynamics relationships

Cardiovascular Effects

The wording proposed by the MAH regarding the QT interval prolongation associated with haloperidol was considered to be acceptable.

Therapeutic Concentrations

The recommendation for a therapeutic concentration range of 1 to 10 ng/ml is supported by clinical study data by Ulrich et al. (1998)[6], Van Putten et al. (1992)[7], Volavka et al. (1992[8], 1996[9]), Jibiki et al. (1993)[10], and Kapur et al. (1997)[11]. Further supporting data derive from Fitzgerald (2000)[12], Nyberg (1995)[13] and Panagiotidis (2007)[14]. With regard to the proposal of a decreased treatment dose

[4] Kelly JF, Soncrant TT, Midha KK, Hubbard JW, McKay G, Rapoport SI. Pharmacokinetics of intravenous haloperidol in healthy young and old subjects. Clin Pharmacol Ther. 1993;53(2):192.
[5] Chang WH, Jann MW, Chiang TS, Lin HN, Hu WH, Chien CP. Plasma haloperidol and reduced haloperidol concentrations in a geriatric population. Neuropsychobiology. 1996;33(1):12-16.
[6] Ulrich S, Neuhof S, Braun V, Meyer FP. Therapeutic window of serum haloperidol concentration in acute schizophrenia and schizoaffective disorder. Pharmacopsychiatry. 1998;31(5):163-169.
[7] Van Putten T, Marder SR, Mintz J, Poland RE. Haloperidol plasma levels and clinical response: a therapeutic window relationship. Am J Psychiatry. 1992;149(4):500-505.
[8] Volavka J, Cooper TB, Czobor P, et al. Haloperidol blood levels and clinical effects. Arch Gen Psychiatry. 1992;49(5):354-361.
[9] Volavka J, Cooper TB, Czobor P, Meisner M. Effect of varying haloperidol plasma levels on negative symptoms in schizophrenia and schizoaffective disorder. Psychopharmacol Bull. 1996;32(1):75-79.
[10] Jibiki I, Kubota T, Fujimoto K, et al. Effective clinical response at low plasma levels of haloperidol in Japanese schizophrenics with acute psychotic state. Jpn J Psychiatry Neurol. 1993;47(3):627-629.
[11] Kapur S, Zipursky R, Roy P, et al. The relationship between D2 receptor occupancy and plasma levels on low dose oral haloperidol: a PET study. Psychopharmacology. 1997;131(2):148-152.
[12] Fitzgerald CH. A double-blind comparison of haloperidol with perphenazine in acute psychiatric episodes. Current Therapeutic Research 1969;11(8):515–519.
[13] Nyberg S, Farde L, Halldin C, Dahl ML, Bertilsson L. D2 dopamine receptor occupancy during low-dose treatment with haloperidol decanoate. Am J Psychiatry. 1995;152(2):173-178.

for schizophrenia, a therapeutic range of 1 to 10 ng/ml is supported based on study data and pertinent Therapeutic Drug Monitoring (TDM) guidance, and is also in line with the AGNP Consensus Guidelines (2011).

The therapeutic effect of antipsychotics and adverse event profile is based on their ability to bind D2-receptors. The relationship between dopamine receptor 2 occupancy (D2RO) and haloperidol concentrations indicate that plasma concentrations as low as 0.6 to 3.2 ng/mL are sufficient for therapeutic response in patients with schizophrenia. It is estimated that D2RO between 60% and 80% is required for a therapeutic effect, without an increased incidence of adverse events, including EPS (Gieglin 2010[15]; Kapur 2000[16]). On average, concentrations in this range would be obtained with doses of 1 to 4 mg daily. It is advised that the high inter-subject variability in haloperidol pharmacokinetics should be considered when giving dosing recommendations, and that drug monitoring should be considered in some cases.

The final agreed wording for this section of the SmPC can be found in Annex III of the CHMP opinion.

Section 5.3 – Preclinical safety data

Evidence from data from preclinical studies, suggest a causal relationship between elevated prolactin levels and the formation of mammary gland tumours, and treatment with D2 receptor antagonists, in rodents. The mammary/breast response to prolactin in humans is similar to that of rats and therefore, prolactin-induced mammary carcinogenesis in the rat carcinogenicity studies may also be relevant to humans, although this relationship has not been ultimately confirmed in humans. This has been adequately reflected in this section.

In accordance with the proposal of recommended doses in patients with acute and maintenance treatment of schizophrenia, a revised therapeutic range of 1 to 10 ng/ml has been taken into consideration to describe the safety margin for cardiotoxic effects in this section. As a result, lowering the therapeutic effective range for haloperidol increases the safety margin for clinically relevant QT prolongation. The changes in the wording on preclinical cardiotoxicity rely on *in vivo* data in the dog.

The final agreed wording for this section of the SmPC can be found in Annex III of the CHMP opinion.

Package Leaflet (PL)

The changes to the SmPC, when relevant for the user, have also been reflected in the PL and endorsed by the CHMP.

2.3. Risk Management Plan

The CHMP did not require the MAH to submit a risk management plan.

3. Expert consultation

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

[14] Panagiotidis G, Arthur HW, Lindh JD, Dahl ML, Sjoqvist F. Depot haloperidol treatment in outpatients with schizophrenia on monotherapy: impact of CYP2D6 polymorphism on pharmacokinetics and treatment outcome. Ther Drug Monit. 2007;29(4):417-422.

[15] Giegling I, Drago A, Schäfer M , Möller H-J, Rujescu D, Serretti A. Interaction of haloperidol plasma level and antipsychotic effect in early phases of acute psychosis treatment. J of Psychiatric Res (2010) 44 487–492.

[16] Kapur S, Robert Z, Jones C, Remington G, and Houle S. Relationship Between Dopamine D2 Occupancy, Clinical Response, and Side Effects: A Double-Blind PET Study of First-Episode Schizophrenia. April 2000. J Psychiatry 157:4.

other depressant medicinal products, and whether there are 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 below.

4. Recommendation

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 and having noted the 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 postmarketing 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 guidelines.

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.

The final agreed wording of the product information can be found in Annex III of the CHMP opinion.

5. Grounds for 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).