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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 and associated names

Active substance: haloperidol

Procedure number: EMEA/H/A-30/1393

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 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 and associated names, in order to resolve divergences amongst the nationally authorised product information and thus harmonise the product information across the European Union (EU).

The scope of this procedure concerns Haldol tablets (1, 2, 4, 5, 10, and 20 mg), oral solutions (2 mg/ml and 10 mg/ml) and injectable solution (5 mg/ml).

2. Scientific discussion

2.1. Introduction

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.

The approved pharmaceutical forms of Haldol in the European Union (EU) are tablet (1, 2, 4, 5, 10, and 20 mg), oral solution (2 mg/ml and 10 mg/ml) and injectable solution (5 mg/ml). Haldol 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 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. Evaluation

2.2.1. Product information

Section 4.1 – Therapeutic Indications

Adults

Schizophrenia

Oral formulation

Haldol (oral formulation) is approved for the indication schizophrenia in 19 European Union (EU)/European Economic Area (EEA) Member States. Not all Member States specifically state the indication *"schizophrenia"* but use more general terms like *"psychotic conditions"* also including organic and affective psychosis, as well as acute episodes of psychosis that do not become chronic.

To support the indication concerning treatment of schizophrenia in adult patients with oral Haldol, the marketing authorisation holder (MAH) provided data from two MAH-sponsored, randomized, placebo-controlled trials, and one large Cochrane review comparing haloperidol to placebo in the adult schizophrenic population. Of the two MAH-sponsored trials, one included patients with schizophrenia, and the other included patients with chronic schizophrenia. Both studies utilised the Diagnostic and Statistical Manual of Mental Disorders (DSM –III) criteria for diagnosis. The review data also included patients with schizophrenia-like diseases. It was shown that haloperidol is effective in the acute treatment of schizophrenia compared to placebo.

There is a significant amount of literature on the use of haloperidol in schizoaffective disorders, and schizoaffective treatment data are almost exclusively provided as sub-group analyses from schizophrenia trials. Taking into consideration the available data and having taken note of the NICE guidelines on the treatment of schizophrenia, the CHMP considered that the benefit/risk balance is positive in the treatment of schizoaffective disorder, and that it should be included in the schizophrenia indication for the oral formulation of haloperidol.

As schizophrenia is a chronic condition and efficacy in schizophrenia includes treatment of acute symptoms and maintenance therapy, inclusion of additional wording "*prevention of relapse of schizophrenia"* was considered not justified.

Taking into account all the available data and the extensive experience with this antipsychotic medication in schizophrenic patients, the proposed harmonised SmPC *wording 'Treatment of schizophrenia and schizoaffective disorder'* for oral formulations of haloperidol was endorsed by the CHMP.

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

Injectable formulation

A harmonised wording for the injectable formulation in schizophrenia was not provided by the MAH since injectable haloperidol is not administered in this indication.

Delirium

Oral formulation

Oral Haldol is currently approved in 8 Member States for the treatment of delirium-like conditions with different wording, e.g. acute confusion or delirium or organic psychosis. Ten Member States use a different indication wording (other psychosis, acute psychosis).

The MAH provided data from three randomized, placebo-controlled trials and nine active comparator trials, which evaluated the efficacy of oral and injectable Haloperidol in the treatment of delirium, to support this indication.

Haloperidol has been found to be effective in lower doses throughout the active-controlled studies, similar to the comparator drug (atypical antipsychotics). This is in line with findings of a Cochrane review by Lonergan (2007)[1], where the author concluded that there is no evidence that a low dosage haloperidol has different efficacy in comparison with the atypical antipsychotics olanzapine and

[1] The Cochrane Collaboration. Lonergan E, Britton AM, Luxenberg J, Wyller TAntipsychotics for delirium (Review). 2007

risperidone in the management of delirium, or has a greater frequency of adverse drug reactions than these drugs. The results from placebo-controlled studies are not convincing of an effect in subjects suffering delirium but the limitations of these trials were acknowledged by CHMP in view of the difficulties to conduct adequate clinical trials in this indication.

In view of the available data, the proposed harmonised SmPC wording for oral formulations of haloperidol; *'Acute treatment of delirium when non-pharmacological treatments have failed'* was endorsed by the CHMP.

Injectable formulation

Haldol (injectable formulation) is approved for use in patients with Delirium (Acute Confusion) in 7 EU/EEA Member States.

The review of the studies provided by the MAH revealed only one placebo-controlled study supporting the intramuscular (IM) injection formulation of haloperidol. Hu et al. (2004)[2] reports on a treatment study with a placebo arm, and also one in which rescue medication with an antipsychotic was not allowed.

In addition, three active-comparator controlled studies provided by the MAH (Breitbart et al. 1996[3], Atalan et al. 2013[4] and Lim et al. 2010[5]) support the IM haloperidol in the treatment of delirium.

The clinical guidelines suggest that there should first be a non-pharmacological approach, identifying and managing underlying causes, providing reorientation, and involving family and caregivers. Therefore the MAH's proposal to specify in the indication that the failure of non-pharmacological treatment should precede the use of Haldol was agreed by the CHMP. Taking into account the clinical guidelines (e.g. NICE 2010[6]) and the maximum duration of the submitted clinical studies (known efficacy/safety data), the acute treatment of this condition has been included in the indication in the SmPC text to read: *'Acute treatment of delirium when non-pharmacological treatments have failed'*.

The indications for the prevention of delirium and post-operative delirium were not pursued further by the MAH due to the lack of supporting data.

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

Mania associated with bipolar I disorder

Oral formulation

Oral Haldol is approved for the indication mania associated with bipolar I disorder (BD) in 15 EEA Member States.

The MAH presented the published results of six placebo-controlled studies and eleven active-controlled studies, conducted in patients with manic episodes in bipolar I disorder. Efficacy was assessed by the use of the YMRS, MRS or BPRS and further secondary efficacy instruments (e.g. CGI-BP, CGI-S, HAMD, BPRS). The results of the six placebo-controlled studies demonstrate the superiority of haloperidol over

[2] Hu H, Deng W, Yang H. A prospective random control study comparison of olanzapine andxx haloperidol in senile delirium. Chongging Medical Journal. 2004;8:1234–1237.
[3] Breitbart W, Marotta R, Platt MM. A double-blind trial of haloperidol, chlorpromazine, and lorazepam in the treatment of delirium in hospitalized AIDS patients. Am J Psychiatry. 1996;153(2):231-237.
[4] Atalan N, Efe Sevim M, Akgun S et al. Morphine is a reasonable alternative to haloperidol in the treatment of postoperative hyperactive-type delirium after cardiac surgery. J Cardiothorac Vasc Anesth. 2013;27(5): 933-938.
[5] Lim H K, Kim J J, Pae C U, Lee C U, Lee C, Paik I H. Comparison of risperidone orodispersible tablet and intramuscular Haloperidol in the treatment of acute psychotic agitation: a randomised open, prospective study. Neuropsychobiology 2010;62:81-86 DOI: 10.1159/000315437
[6] NICE clinical guideline 100. Alcohol-use disorders: Diagnosis and clinical management of alcohol related physical complications. 2010

placebo and are therefore in support of the proposed indication. This conclusion is additionally supported by a meta-analysis of these studies (Cipriani et al. 2006[7]; Cochrane review).

Direct head-to-head comparison studies of haloperidol exist with olanzapine (Tohen et al. 2003[8]), aripiprazole (Vieta et al. 2005[9]), valproate (McElroy et al. 1996[10]), carbamazepine (Brown et al. 1989[11]) and lithium (Segal et al. 1998[12]) and in combination with lithium vs. carbamazepine/lithium (Small et al. 1995[13]). These studies also support an antimanic effect of haloperidol in various subtypes of mania.

In addition, the World Federation of Societies of Biological Psychiatry (WFBSP)[14] updated guidance on mania treatment states that haloperidol has been used as a comparator in randomized, placebo-controlled studies examining risperidone, quetiapine, ziprasidone, aripiprazole and in a combination study of risperidone with lithium or valproate. In all these studies, haloperidol was shown to be significantly better than placebo.

The proposed harmonised SmPC wording "*Treatment of moderate to severe manic episodes associated with bipolar I disorder*" was endorsed by the CHMP based on the results of the reviewed placebo-controlled studies with oral haloperidol. As safety data revealed a higher propensity to provoke a switch to depression with haloperidol than with other atypical antipsychotics, Haldol is not indicated for continued use but only for acute use in manic episode until remission.

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

Injectable formulation

Haldol (injectable formulation) is currently approved for the indication mania associated with BD in 10 of the EU/EEA Member States.

No data were submitted in support of an indication for the injectable formulation as a specific claim for the injectable formulation of haloperidol in mania associated with bipolar I disorder was not proposed by the MAH.

Psychomotor agitation associated with psychotic or bipolar disorder

The MAH provided supportive data from a Cochrane review and based the discussion on 21 (out of 32) randomised controlled trials. The Cochrane review (up to year 2011; Powney et al. 2012[15]) described the effectiveness of haloperidol alone, administered orally, IM or IV compared to placebo or another antipsychotic. In addition four active comparator controlled studies have been provided to support the use of haloperidol in the treatment of psychomotor agitation.

Oral formulations

[7] Cipriani A, Rendell JM, Geddes J. Haloperidol alone or in combination for acute mania (Review). published in The Cochrane Library 2006, Issue 3.
[8] Tohen M et al. A 12-Week, double-blind comparison of olanzapine versus haloperidol in the treatment of acute mania. Arch Gen Psychiatry.2003; 60: 1218-1226.
[9] Vieta E et al. Effectiveness of aripiprazole versus haloperidol in acute bipolarmania Double-blind, randomised, comparative 12-week trial. British j psych. 2005; 187: 235-242.
[10] McElroy S L et al. A randomized comparison of divalproex oral loading versus haloperidol in the initial treatment of acute psychotic mania. J Clin Psych. 1996; 57(4): 142-146.
[11] Brown D. et al. Carbamazepine compared to haloperidol in acute mania. Inter. Clin. Psychopharma. 1989; 4(3):229-238.
[12] Segal et al. Risperidone Compared with both lithium and haloperidol in mania:A double-blind randomized controlled trial. Clin Neuropharml.1998;21(3):176-180.
[13] Small JG, Klapper MH, Marhenke JD, Milstein V, Woodham GC, Kellams JJ. Lithium combined with carbamazepine or haloperidol in the treatment of mania. Psychopharmacol Bull. 1995;31(2):265-72.
[14] The World Federation of Societies of Biological Psychiatry (WFSBP) Guidelines for the Biological Treatment of Bipolar Disorders: Update 2012 on the long-term treatment of bipolar disorder Grunze H, Vieta E, GUY M. Goodwin G M, Bowden C, Licht R W6 , Öller H-J, Kasper S on behalf of the WFSBP Task Force on Treatment Guidelines for Bipolar Disorders. The World Journal of Biological Psychiatry, 2013; 14: 154–219
[15] Powney MJ, Adams CE, Jones H. Haloperidol for psychosis-induced aggression or agitation (rapid tranquillisation) (Review). Cochrane Libr. 2012;11.

Oral Haloperidol is approved for the indication psychomotor agitation in 10 EU/EEA Member States.

The evidence for the oral formulation in this indication is limited, but the available data was found to be supportive. In five comparator controlled randomised trials investigating the emergency management of agitated patients, oral haloperidol proved to be approximately equally efficacious as orally administered lorazepam (Foster 1997[16]) or second generation antipsychotics (SGAs) (Kinon 2004[17]; Villari 2008[18]; Walther 2014[19]), and parenterally administered (IM or IV) haloperidol (Foster 1997[20]; Möller 1982[21]).

Haloperidol is considered of value in the acute treatment of agitation in clinical practice, even though the safety profile may limit its use in some patients due to adverse drug reactions such as extrapyramidal symptoms (EPS) and sedation. The current treatment guidelines and expert opinion agree that oral formulations should be offered in the first instance, if clinically feasible (Allen 2005[22]; APA 2004[23]; Macpherson 2005[24]; NICE 2005[25]). If these are refused or are inappropriate, medication should be administered parenterally.

Based on the available data, the MAH's proposal to include the patients experiencing agitation associated with psychotic and bipolar I disorder was revised and agreed as follows: *'Treatment of acute psychomotor agitation associated with psychotic disorder or manic episodes of bipolar I disorder'.*

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

Injectable formulation

Injectable Haldolis approved for use in patients with psychomotor agitation in 9 EU/EEA Member States.

The placebo-controlled experience with haloperidol in the treatment of agitation in the course of schizophrenia or bipolar disorder is limited and haloperidol was solely given IM. This was also largely the case for the active-controlled trials reviewed. The population with agitation in the course of bipolar disorder was reported in a few studies only (Baldacara et al (2011)[26], Taymeeyapradit et al. (2002)[27], Bailine et al. (1987)[28], Kewala et al. (1984)[29], and Battaglia et al. (2003)[30]), where efficacy could be demonstrated and the indication supported.

[16] Foster S, Kessel J, Berman M E & Simpson G M. Efficacv of lorazeoam and halooeridol for rapid ttanquilization in a psychiatric emergency room settingInnreniational Clinical Psychophamzacolo~(19 97), 12, 175-179
[17] Kinon B J, Ahl J, M D Rotelli & McMullen M. Efficacy of Accelerated Dose Titration of Olanzapine With Adjunctive Lorazepam to Treat Acute Agitation in Schizophrenia. Am J Emerg Med. 2004 22(3): 181-186
[18] Villari V. Rocca P, Fonzo V Montemagni C, Pandullo P, Bogetto F. Oral risperidone, olanzapine and quetiapine versus haloperidol in psychotic agitation. Progress in Neuro-Psychopharmacology & Biological Psychiatry 32 (2008) 405–413.
[19] Walther S, Moggi F, Horn He, Moskvitin K, Abderhalden C, Maier N, Strik W, and Mu¨ ller T J. 2014. Rapid Tranquilization of Severely Agitated Patients With Schizophrenia Spectrum Disorders. J of Clin Psychopharm. Vol 34(1)
[20] Foster S, Kessel J. Berman M E and Simpson G M. Efficacv of lorazeoam and halooeridol for rapid tanquilization in a psychiatric emergency room setting. Int Clin Psychopham (1997), 12, 175-179.
[21] Möller H-J, Kissling W, Lang C, Doerr P, Pirke K-L and Zersson D V. Efficacy and side effects of haloperidol in psychotic patients: oral versus intravenous administration. 1982. Am J Psychiatry 139(12), 1571-1575
[22] Allen M H, Currier G W, Carpenter D, Ross R W, Docherty J P. 2005. J Psychiatric Prac Vol. 11(1), 5-25.
[23] Practice Guideline For The Treatment of Patients With Schizophrenia Second Edition
[24] Macpherson R, Dix R & Morgan S. A growing evidence base for management Guidelines. Advances in Psychiatric Treatment (2005), vol. 11, 404–415.
[25] NICE Clinical Practice Guidelines. Violence clinical practice guidelines: The short-term management of disturbed/violent behaviour in in-patient psychiatric settings and emergency departments. 2005
[26] Baldaçara L, Sanches M, Cordeiro DC, Jackoswski AP. Rapid tranquilization for agitated patients in emergency psychiatric rooms:a randomized trial of olanzapine, ziprasidone, haloperidol plus promethazine, haloperidol plus midazolam and haloperidol alone. Rev Bras Psiquiatr. 2011;33(1):30-39 (N290758).
[27] Taymeeyapradit U, Kuasirikul S. Comparative study of the effectiveness of zuclopenthixol acetate and haloperidol in acutely disturbed psychotic patients. Journal of the Medical Association of Thailand. 2002;85(12):1301–1308.
[28] Bailine, SH, Lesser MS, Krubit G, Ravasz TJ, Davies RA, Kane JM. Comparison of IM haloperidol and IM chlorpromazine in the treatment of acutely psychotic patients. Psychiatr Hosp. 1987;18(3):127-129.
[29] Kewala S, Ban TA, Berney SA, Wilson WH. Rapid tranquilization: A comparative study of thiothixene and haloperidol. Prog Neuropsychopharmacol Biol Psychiatry. 1984;8: 77–83.

Rapid tranquillisation is needed in situations requiring the rapid control of agitation, aggression or excitement in adult psychiatric inpatients, where de-escalation techniques have not proved sufficient in themselves, and cooperation from the patient in taking oral medication may be difficult. Parenteral administration of medication to control the behaviour and obtain tranquillity is therefore usually needed in the very early period of treatment.

Based on submitted clinical documentation and current guidelines, the revised indication agreed by the CHMP is: *"Rapid control of severe acute psychomotor agitation associated with psychotic disorder or manic episodes of bipolar I disorder when oral therapy is not appropriate."*

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

Psychotic symptoms, suspiciousness, hostility and impulsive behaviour associated with borderline and schizotypal personality disturbances

Oral formulations

Haldoll (oral formulation) is approved for the indication personality disorders (PD) in only 4 EU/EEA Member States.

The MAH provided data of three placebo-controlled trials and two active comparator controlled studies assessing the efficacy and safety of oral haloperidol in the treatment of borderline and schizotypal personality disorders. As a result no differences in efficacy of haloperidol and second generation antipsychotics could be found in the comparator studies reviewed while a tendency towards an increase in depression was reported. Overall the safety profile of haloperidol has been poorly characterised in the provided studies.

There is a lack of robust and reproducible data on symptoms prevailing in borderline and/or schizotypal personality disorders (irritability, impulsivity, aggression) and methodology as well as high drop-out rates to support this proposed indication. There appears to be no evidence for any PD itself, as symptoms related to a PD (irritability, aggression etc.) may often occur due to comorbidity rather than due to the PD itself. Common guidance documents and reviews (WFSBP, NICE, Cochrane review 2010) do not recommend haloperidol as a treatment option in this condition. The totality of data, including a lack of long-term experience (max. duration was 16 weeks in clinical studies, whereas PD may have a life-long prevalence, which would require long-term treatment), this indication was therefore not endorsed by the CHMP.

Based on the lack of sufficient data with regard to adverse effects or of the benefit of long-term treatment the MAH agreed to delete this indication.

Injectable formulation

Haldol (injectable formulation) is approved for the indication personality disorders in only two EU/EEA Member States where it is currently approved.

No data were submitted by the MAH in support of an indication for the injectable formulation.

Agitation, aggression and psychotic symptoms associated with dementia

Oral formulations

[30] Battaglia J, Lindborg SR, Alaka K, Meehan K, Wright P. Calming versus sedative effects of intramuscular olanzapine in agitated patients. Am J Emerg Med. 2003;21(3):192–198.

Haloperidol oral formulation is approved for the treatment of behavioural symptoms in patients with dementia in 12 EU/EEA Member States.

The MAH referenced to nine studies (Sugarman 1964[31], Petrie 1982[32], De Deyn et al. 1997[21], Devanand et al. 1998[19], Allain et al., 2000[22], Teri et al., 2000; Chan et al., 2001; Suh et al., 2004 Tariot et al., 2006) studying the effects of Haloperidol in agitation, aggression (the second being often studied as a subdomain of the first), and psychotic symptoms in patients with dementia. For the psychotic symptoms, and particularly with reference to the studies of Sugarman, Devanand and Petrie, and with some degree of extrapolation from the treatment of the same symptomatic dimension in other diseases, the efficacy has also been considered sufficiently demonstrated.

With regards with the specific behavioural symptoms to be included in the indication, while there is sufficient evidence to support the efficacy of Haloperidol for aggression, the same cannot be concluded for agitation. This is in line with the results of a Cochrane review by Lonergan et al. (2002) and with the conclusions of the SAG. The term “agitation” is also not supported by the S3 guidance on dementia (by German Society of Neurology and the German Association for Psychiatry, Psychotherapy and Psychosomatics in association, 2009).

With regards to the severity and type of dementia, the indication was restricted to moderate to severe Alzheimer’s Disease and Vascular Dementia in the light of the characteristics of the population recruited in the trials reviewed, the specific concerns of the dopamine-related mechanism of action for haloperidol in other types of dementia, and in accordance with the advice of the SAG.

Comments received from some of the HCPOs on the use of haloperidol in this indication (European Society of Anaesthesiology, European Psychiatric Association and European College of Neuropsychopharmacology) ranged from “not recommended” to “not frequently used”.

Based on all available data, the MAH has included wording adequate that haloperidol should be administered in this indication when non-pharmacological treatments have failed. This implies persistency of symptoms. As rating scales are not practical in clinical settings, the most important clinical criteria to be met before treatment is initiated is whether the behaviour is persistent and whether the symptoms places the person or carer at risk of harm. The administration has therefore been restricted to persistent symptoms, rather than severe, when there is a risk of harm to person or others.

The revised indication stating the need for treatment re-evaluation after no more than 6 weeks was endorsed by the CHMP:

‘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’.

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

Injectable formulation

Haldol injectable formulation is approved for the treatment of patients with dementia in 7 EU/EEA Member States.

[31] Sugerman A A, Williams B H, Alderstein A M. Haloperidol in the psychiatric disorders of old age. 1964. Am J Psychiatry. 120(12), 1190-1192.
[32] Petrie W M, Ban T A, Berney S, Fujimori M, Guy W, Ragheb M, Wilson W H,' and Schaffer D. and Schaffer J D. Loxapine in Psychogeriatrics: A Placebo- and Standard-Controlled Clinical Ïnvestigation. 1982. J Clin Psychopharm 2-, p 122-126,

As there are no studies that have evaluated the efficacy and safety of injectable formulations for this indication, the MAH considers that there is insufficient data to support the indication and posology for the injectable formulation. The indication has therefore been removed from the SmPC.

Tic disorders, including Tourette's syndrome (TS)

Oral formulations

Haldol (oral formulation) is approved for the indication Tourette syndrome in 11 EU/EEA Member States. Nine of these Member States also have the indication" Tics".

The MAH provided a review of a total of 3 placebo-controlled studies evaluating haloperidol in patients with Tic disorders including Tourette syndrome. The only study demonstrating efficacy was described by Shapiro et al. 1989[33], but was not evaluated by age groups. The study of Ross et al. 1978[34] is too small to firmly assess efficacy, and the results in the study of Sallee et al. 1997[35] failed to show efficacy of haloperidol.

The European clinical guidelines for Tourette syndrome (Roessner et al., 2011[36]) - provided reference by the European Society for the Study of Tourette Syndrome (ESSTS) - recommend that non-pharmacologic and/or pharmacologic interventions should be considered in addition to psychoeducation for persons with clear impairment associated with the tics. The European guideline includes an evaluation of the level of evidence (Haloperidol is graded A on a scale from A being the best available level of evidence to C being the lowest) and an expert rating in which haloperidol scores behind other antipsychotics (including Second Generation Antipsychotics) and the alpha-2 agonist Clonidine.

SAG experts, also in consideration of the above mentioned evidence and reviews, advised to retain an indication referring to subjects of at least 10 years of age presenting with major limitations/disabilities in subjective, social, emotional and functional domains in whom non-pharmacological and pharmacological treatments have failed. Comments received from some HCPOs also supported the use of Haloperidol as a second/third line treatment option.

Taking all into consideration the above, the CHMP agreed that this indication should be retained for oral haloperidol, for treatment of more severe forms of Tics and Tourette Syndrome. However non-pharmacologic and/or pharmacologic interventions and psychoeducation should first be considered as an important first step in treatment of Tourette Syndrome. The indication has been revised to read: *'Treatment of tic disorders, including Tourette's syndrome, in patients with severe impairment after educational, psychological and other pharmacological treatments have failed'*.

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

Injectable formulation

Haloperidol injectable formulation is approved for use in patients with Tourette disorder in 4 EU/EEA Member States. Three of these Member States have the indication Tics also. Four Member States mention only the indication Tics and not specifically Tourette disorder.

[33] Shapiro E, Shapiro A, Fulop G, Hubbard M, Mandeli J, et al.Controlled study of haloperidol, pimozide, and placebo in the treatment of Gilles de la Tourette's Syndrome. Arch Gen Psychiatry. 1989;46:722–730.
[34] Ross MS, Moldofsky H. A comparison of pimozide and haloperidol in the treatment of Gilles de la Tourette's Syndrome. Am J Psychiatry. 1978;135(5): 585–587.
[35] Sallee FR, Nesbitt L, Jackson C. Relative Efficacy of Haloperidol and Pimozide in Children and Adolescents With Tourette's Disorder. Am J Psychiatry. 1997;154:1057-1062.
[36] Roessner V, Plessen KJ, Rothenberger A et al. European clinical guidelines for Tourette syndrome and other tic disorders. Part II: pharmacological treatment. Eur Child Adolesc Psychiatry. 2011;20:173–196.

The MAH considers that there is insufficient data to support the indication and posology for the injectable formulation, as there are no studies available to support a harmonised indication. Therefore a harmonised indication for the injectable formulation was not agreed by the CHMP.

Choreatic movement disorders, including Huntington's disease

Oral formulation

Haldol oral formulation is approved for the treatment of choreatic movements in 8 EU/EEA Member States.

The MAH submitted three publications (Burgunder 2011[37], Frank 2014[38], Priller 2008[39]) with regard to the significant value of haloperidol in the treatment of Chorea Huntington. Although other treatments (tetrabenazine and tiapride) have a role prior to the use of haloperidol, it has been acknowledged (Frank 2014[44]) that there is a certain benefit of haloperidol in subjects concomitantly suffering from psychosis, aggression and impulsivity.

Guidelines do not provide a general recommendation for the use of haloperidol in this condition although the Maudsley Prescribing Guidelines express that there is some efficacy of haloperidol when the Chorea Huntington is mild to moderate. As the disease progresses, typical antipsychotics tend to be poorly tolerated due to dystonia and parkinsonism.

Taking all available data into account including clinical studies, clinical relevance and expert comments, the proposal to retain the indication for the oral formulation was agreed by the CHMP. The wording of the indication was slightly modified to reflect the acceptable benefit risk for subjects with mild to moderate choreatic movement disorders in Huntington's disease and taking into consideration the place in the therapeutic strategy of tetrabenazine and tiapride (see Maudsley Prescribing Guidelines): *'Treatment of mild to moderate chorea in Huntington's disease, when other medicinal products are ineffective or not tolerated'*.

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

Injectable formulation

Haldol injectable formulation is approved for use in patients with choreatic movements in 5 of the 14 EU/EEA Member States.

There are no specific clinical studies that support the injectable formulation of haloperidol in this indication. The MAH argued for the clinical value of injectable haloperidol in the treatment of choreatic movement disorders, including Huntington's disease, when other medicinal products are ineffective or not tolerated, or when oral treatment is not possible given that difficulties in swallowing and aggression are often associated with Huntington's disease. The CHMP accepted the MAH's arguments and taking into account the comments from the HCPOs that haloperidol is used in this condition (albeit rarely), the indication wording for injectable and oral haloperidol was revised to indicate that haloperidol has been evaluated for choreatic symptoms in Huntington's disease only: *'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'*.

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

[37] Burgunder J-M, Guttman M, Perlman S, Goodman N, van Kammen P D., and LaVonne and Goodman. An International Survey-based Algorithm for the Pharmacologic Treatment of Chorea in Huntington's Disease. 2011. Version 2. PLoS Curr. August 30 [revised 2011 October 11]; 3: RRN1260

[38] Frank S. 2014. Treatment of Huntington's Disease. (2014) Neurotherapeutics 11:153–160

[39] Priller J, Ecker D, Craufurd D. A Europe-Wide Assessment of Current Medication Choices in Huntington's Disease. 2008. 23(12), , pp. 1788–1792.

As an adjunct to benzodiazepines in the treatment of delirium, delusions or hallucinations in alcohol withdrawal syndrome

Oral formulations

Haldol (oral formulation) is approved for the indication Alcoholism in 4 of the 18 EU/EEA Member States.

There are no studies on the use of the oral haloperidol "*as an adjunct to benzodiazepines in the treatment of delirium, delusions or hallucinations in alcohol withdrawal syndrome*" and no harmonised SmPC wording was proposed by the MAH. Therefore the use of haloperidol in this indication for the oral formulations was not agreed by the CHMP.

Injectable formulation

Haldol (injectable formulation) is approved for the indication Alcoholism in 2 EU/EEA Member States only.

Because antipsychotic agents are not effective for treating the underlying alcohol withdrawal state, they should be used as an adjunct to benzodiazepines. Two active-controlled studies (comparison of haloperidol with mesoridazine and hydroxyzine; haloperidol add-on with benzodiazepines), using haloperidol as IM injection were provided. Of these, only the study by Spies et al. 199640 reports on haloperidol as an adjunct to a benzodiazepine (groups were flunitrazepam/clonidine, chlormethiazole/haloperidol, or flunitrazepam/ haloperidol). The results of the primary outcome measures of this study led to the conclusion that flunitrazepam/haloperidol should be preferred in patients with cardiac or pulmonary risk.

The data provided in support of the proposed indication "*as an adjunct to benzodiazepines in the treatment of delirium, delusions or hallucinations in alcohol withdrawal syndrome*" is very limited. The MAH agrees that benzodiazepines and not antipsychotics are considered the first choice for the treatment of alcohol withdrawal syndrome, according to the Maudsley prescribing guidelines (10th Edition - Taylor 2015) and American Psychiatric Association (APA) practice guidelines for the treatment of patients with substance use disorders (2006; Second edition).

Apart from these studies, no substantive additional data to support the indication were identified. As a consequence, the MAH proposed to remove this indication from the SmPC – this was endorsed by the CHMP.

Agitation in acute alcohol intoxication

Oral formulation

Haldol (oral formulation) is approved for the indication Alcoholism in 3 of the 18 EU/EEA Member States.

There are no studies on the use of the oral haloperidol in "*Agitation in acute alcohol intoxication*" and a harmonised indication for the injectable formulation was not proposed by the MAH. Therefore the use of haloperidol in this indication for the oral formulations was not agreed by the CHMP.

Injectable formulation

Haldol (injectable formulation) is approved for the indication Alcoholism in 2 of the 18 EU/EEA Member States only.

[40] Spies CD, Dubisz N, Neumann T et al. Therapy of alcohol withdrawal syndrome in intensive care unit patients following trauma: results of a prospective, randomized trial. Crit Care Med. 1996;24(3):414-422.

One placebo-controlled trial has been provided using 5 or 10 mg of IM haloperidol, where evaluation has been performed on responders only. An active controlled trial reported on efficacy of haloperidol vs. diazepam. From the data provided no conclusion can be made on the difference between haloperidol and diazepam. Safety aspects have not been reported (Cohen 1974[41]). A second comparative trial by Gibson (1974)[42] with haloperidol and chlordiazepoxide concluded efficacy to be superior for haloperidol in nausea only. The drop-out rate was 14 of 16 patients with haloperidol and 13 of 16 patients with chlordiazepoxide. Therefore, based on the weak data from small clinical trials, this indication is not supported.

The MAH agrees that benzodiazepines and not antipsychotics are considered the first choice for the treatment of alcohol withdrawal syndrome, according to the Maudsley Prescribing Guidelines (10th Edition - Taylor 2015) and American Psychiatric Association (APA) practice guidelines for the treatment of patients with substance use disorders (2006; Second edition). Apart from the studies mentioned above, no substantive additional data to support the indication were identified. Most of the HCPOs consulted, as well as the SAG, did not recommend Haloperidol in this condition. As a consequence, the MAH agreed to remove this indication from the SmPC.

Anti-emetic

Oral formulations

Haldol (oral formulation) is approved as antiemetic in 12 EU/EEA Member States.

Since oral medications are usually ineffective if the patient is vomiting, a harmonised indication for the oral formulation was not proposed by the MAH. There were no studies that evaluated oral haloperidol in post-operative nausea and vomiting (PONV). Therefore the use of haloperidol in this indication for the oral formulations was not agreed by the CHMP.

Injectable formulation

Haldol injectable formulation is approved as an antiemetic in 11 EU/EEA Member States. The wording differs in some Member States for the nausea and vomiting indication, with restriction to those patients who have not adequately responded to alternatives. Other Member States use the indication of vomiting related to radiotherapy. Haloperidol in PONV is only indicated in 1 member state. In another, no specific origin of emesis is stated.

The MAH proposed the following wording on the treatment/prophylaxis of nausea and vomiting for the injectable formulation only: '*Prophylaxis of postoperative nausea and vomiting' and 'Treatment of established nausea and vomiting of varying origins'.*

Five studies were provided to support the indication for the prophylactic efficacy of haloperidol in chemotherapy-induced emesis. These studies compared haloperidol with metoclopramide, prochlorperazine, droperidol, tetrahydrocannabinol, and benzquinamide and were all lacking a placebo arm. Superiority of haloperidol over the active comparator was reported for all but one study (metoclopramide found to be superior over haloperidol). The quality of the studies and the high drop-out rate do not favour a broad indication.

Seven placebo-controlled studies in patients with emesis associated with gastrointestinal disorders were also reported. Two of the studies failed to show efficacy over placebo. The most notable

[41] Cohen, P.J. A double-blind evaluation of the antiemetic properties of HALDOL in hospitalized patientsfollowing operative procedures. In: McNeil Laboratories, Inc. Haldol® (haloperidol) injection for use as an antiemetic agent. 1974

[42] Mc Neil Laboratories Inc. Dr. G.P. Gibson's double blind study on HALDOL® (haloperidol vs. Librium Chlordiazepoxide) in Acute Brain Syndrome-Alcohol Intoxication. Report Date: July 1974.

shortcomings pertain to the lack of specification of gastrointestinal disorders and the overall small treatment groups.

Therefore the indication *'Treatment of established nausea and vomiting of varying origins'*, which should at least include gastrointestinal disorders (although not specified in clinical studies) and chemotherapy and radiotherapy-induced nausea and vomiting, was not supported from an evidence-based point of view. Several alternatives are available for these conditions.

Furthermore it should be noted that haloperidol ranges among the first generation antipsychotic agents (FGA) with a prominent influence on prolongation of the QT interval (Ozeki 2010[43]), and Torsade de Pointes Arrhythmia has been reported with haloperidol treatment. Alternatives are available for the conditions claimed and taking into account the safety concerns, the indication as anti-emetic was not supported.

Therefore the MAH proposed to restrict the indication for Haldol injection to PONV, thereby limiting the broad indication as an antiemetic.

The MAH provided a review of seven placebo-controlled studies and a meta-analysis for the prophylaxis of PONV. Except for two of these studies, the route of administration was intravenous (IV). Of the five studies that used haloperidol IV (Honarmand et al 2012[44], Chu et al 2008[45], Wang et al 2008[46], Aouad et al 2007[47], and Dyrberg et al 1962[48]), four studies provided data for complete response. Thus the efficacy of haloperidol in the prophylaxis and treatment of PONV has been demonstrated in well-designed placebo-controlled and active-comparator trials. For the remaining two studies using the IM formulation, efficacy was only supported by the study of Tornetta et al. (1974)[49].

Although the majority of the evidence supporting the efficacy of haloperidol in the prophylaxis of PONV comes from studies using the IV route, the complete bioavailability of both formulations and the time to peak concentration of around 15 minutes for the IV formulation, and between 20 and 40 minutes for the IM formulation allow to conclude that both routes of administration are effective. In order to minimize the risks of QTc prolonging effects the MAH recommends IM administration only instead of IV.

In support of the treatment of PONV, the MAH provided six MAH-sponsored placebo-controlled studies (Ritter 1974[50], Cohen 1975[51], Dannemiller 1974[52], DeBakker 1975[53]). Haloperidol was administered as a single intramuscular injection following the onset of postoperative vomiting. Clinically significant

[43] Koide T, Ozeki K, Kaihara S. Etiology of QT prolongation and T wave changes in chronic alcoholism. Jpn Heart J. 1981; 22(2):151-166.
[44] Honarmand A, Safavi M, Khalili G, Mohammadnejad F. Prophylactic administration of haloperidol plus midazolam reduces postoperative nausea and vomiting better than using each drug alone in patients undergoing middle ear surgery. Saudi J Anaesth 2012;6:2, 45-151
[45] Chu C C, Shieh J P, Tzeng J-I, Chen J-Y, Lee Y, Ho S-T, Wang J-J. The Prophylactic Effect of Haloperidol Plus Dexamethasone on Postoperative Nausea and Vomiting in Patients Undergoing Laparoscopically Assisted Vaginal Hysterectomy. 2008 Int Anesthesia Res Soc. 106(5), 1403-1406
[46] Wang T. F, Liu Y. H, Chu C. C, Shieh J. P, Tzeng J. I, Wang J. J. Low-dose haloperidol prevents post-operative nausea and vomiting after ambulatory laparoscopic surgery. Acta Anaesthesiol Scand 2008; 52: 280–284
[47] Apfel C.C, Kranke P, Piper S, Rüsch D, Kerger H, Steinfath M, Stöcklein K, Spahn D.R, Möllhoff T, Danner K, Biedler A. M, Hohenhaus B. Zwissler O. Danzeisen H. Gerber F.-J. Kretz. Nausea and vomiting in the postoperative phase. Anaesthesist 2007 56:1170–1180
[48] V. Dyrberg. Haloperidol (Serenase)in the prevention of postoperative nausea and vomiting. Acta anaesthesiologica Scandinavica, 1962. 6, 37-47.
[49] Tornetta F. A double-blind dose range evaluation of the antiemetic effectiveness of parenteral HALDOL in postoperative patients. In: McNeil Laboratories, Inc. Haldol® (haloperidol) injection for use as an antiemetic agent. 1974
[50] Ritter, R. & Watson R.L. A double-blind evaluation of the antiemetic properties of HALDOL in hospitalized patients following operative procedures. In: McNeil Laboratories, Inc. Haldol® (haloperidol) injection for use as an antiemetic agent. 1974
[51] Barton MD, Libonati M, Cohen PJ. The use of haloperidol for treatment of postoperative nausea and vomiting-a double-blind placebo-controlled trial. Anesthesiology. 1975;42(4):508-512.
[52] Dannemiller FJ. A double blind evaluation of the antiemetic properties of HALDOL in hospitalized patientsfollowing operative procedures. In: McNeil Laboratories, Inc. Haldol® (haloperidol) injection for use as anantiemetic agent. 1974
[53] DeBakker, A. (1) A double-blind evaluation of the antiemetic properties of HALDOL in hospitalized patients following operative procedures. In: McNeil Laboratories, Inc. Haldol® (haloperidol) injection for use as an antiemetic agent. 1974

results for the reduction of nausea and vomiting with haloperidol have been obtained in four of the six studies. However, the currently accepted endpoint of 24 hour postoperative observation has not been included in any of these studies limiting their value to support the indication “treatment in PONV”. However further studies have been presented including a meta-analysis conducted by Büttner (2004)[54] supporting the efficacy of parenteral haloperidol in the prophylaxis and treatment of PONV (not with antiemetic therapy in chemotherapy) to support the indication.

PONV occurs in approximately 30% of patients undergoing surgery. The therapeutic guidelines developed by a German expert committee (Apfel et al, 2007[55]), the French Society of Anaesthesia and Resuscitation (2008), SAMBA (2014), and the Society of Obstetricians and Gynaecologists of Canada (SOGC; Grade II-1 Ab) (2008) do not support the use of antiemetic agents for all surgical patients. These Expert guidelines recommend haloperidol as a second-line PONV prophylaxis for subjects with moderate risk.

HCPOs consulted by CHMP came to the conclusion that there is no relevant need for haloperidol in this indication.

Taking into account the available data and the MAH’s argumentation, the CHMP considered that the MAH had provided sufficient argumentation for retaining the indication on prophylaxis and treatment of postoperative nausea and vomiting (PONV) as a second-line treatment. The different roles of haloperidol in the prophylaxis and treatment have been stated separately as:

‘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.’

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

The following indications were not included in the proposed harmonised as the MAH considered that there was insufficient evidence to support their inclusion: aggression and anti-agitation in mentally retarded patients or patients with organic brain damage, severe pain, singultus (hiccups), stuttering, alcoholism & Korsakoff’s syndrome, torticollis and drug induced dyskinesia and anxiety.

Paediatric population

Schizophrenia

Haloperidol underwent an Article 45 paediatric work sharing procedure in 2010, which was concluded in January 2012. The MAH provided publications including those also submitted for the Article 45 paediatric work sharing procedure: two placebo-controlled studies, four double-blind, active comparator-controlled studies and two open-label active-comparator studies. A recent literature search did not provide additional clinical trial data beyond the former cut-off date 2010 for the Article 45 procedure.

The design of the studies performed with haloperidol in children and/or adolescent with schizophrenia had several shortcomings across the presented trials. One of the placebo-controlled trials (Pool et al.,

[54] Michael Büttner, D.M.D.,* Bernhard Walder, M.D.,† Erik von Elm, M.D., M.Sc.,‡ Martin R. Tramèr. Is Low-dose Haloperidol a Useful Antiemetic? Anesthesiology 2004; 101:1454–63

[55] Apfel C.C, Kranke P, Piper S Rüsch D, Kerger H, Steinfath M, Stöcklein K, Spahn D.R, Möllhoff T, Danner K Biedler A, Hohenhaus M, Zwissler B, Danzeisen O, Gerber H, Kretz F.-J. Nausea and vomiting in the postoperative phase. Anaesthesist 2007 56:1170–1180

1976[56]) could not show efficacy of haloperidol in adolescents at all, except for those with more severe disease. The second placebo-controlled trial (Spencer et al. 1992[57]) in children with schizophrenia could show a certain degree of superiority of haloperidol over placebo; however, the sample size was too small to draw any firm conclusion. Regarding the active-controlled trials presented by the MAH, only short-term antipsychotic treatment was applied. No long-term efficacy/safety studies are available.

Haloperidol is generally not considered a first choice antipsychotic in the treatment of childhood/adolescent schizophrenia. However comments of the HCPOs consulted by CHMP delineate that haloperidol is a valuable part of the treatment armamentarium for schizophrenia in children and adolescents that is needed to individually decide based on the safety differences of different classes of antipsychotics in the respective patient. In addition, the SAG supports this view in children with schizophrenia, although haloperidol is not considered to be a first line treatment in these subjects, but rather a 3rd line treatment, or a 2nd line treatment in patients whose risk profile suggests a high liability to metabolic side-effects of second generation antipsychotics.

Following all the views expressed, the indication for schizophrenia in adolescents aged 13 to 17 years was considered to be acceptable. This age range proposed best complies with the data provided, and is consistent with early-onset schizophrenia and the potential need in clinical practice. Based on all relevant clinical data and noting the expert consultations and therapeutic guideline recommendations, the paediatric indication was revised to refer to the setting where other treatments have failed: *'Schizophrenia in adolescents aged 13 to 17 years when other pharmacological treatments have failed or are not tolerated'.*

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

No proposal was presented for an indication for the injectable formulation of haloperidol since data are lacking. Therefore the use of injectable Haldol in schizophrenia in the paediatric population was not agreed by the CHMP.

Behavioural symptoms such as aggression and impulsive behaviour in children with autism / pervasive developmental disorders

Haloperidol (oral formulation) is approved for use as a psychomotor anti-agitation agent in disorders of behaviour and character in children in 8 EU/EEA Member States where it is currently marketed.

The MAH provided five placebo-controlled studies in children and adolescents with autistic disorder. The respective publications derive mainly from the 1980s and clinical data provided are incomplete. The studies were short-term, with a maximum duration of 12 weeks. Significant decreases in behavioural and maladaptive symptoms such as withdrawal, stereotypies and hyperactivity have been reported under haloperidol treatment. In addition, the MAH provided one 12-week comparator-controlled study (Miral et al., 2008[58]) with risperidone and haloperidol in the treatment of autistic disorder in 30 children. In this study, risperidone appears more efficacious and safer than haloperidol. Except for the placebo-controlled study of Remington et al. 2001[59] and Miral, all other studies included children 2 to 7 years of age.

[56] Pool D, Bloom W, Mielke DH et al. A controlled evaluation of loxitane in seventy-five adolescent schizophrenic patients. Curr Ther Res. 1976; 19: 99-104. LMD11788.
[57] Spencer EK, Kafantaris V, Padron-Gayol MV et al. Haloperidol in schizophrenic children: early findings from a study in progress. Psychopharmacol Bull. 1992; 28: 183-186. LMD91562.
[58] Miral S, Gencer O, Inal-Emiroglu FN et al. Risperidone versus haloperidol in children and adolescents with AD - a randomized, controlled, double-blind trial. Eur Child Adoles Psychiatry. 2008; 17 (1): p.1-8. LMD246871.
[59] Remington G, Sloman L, Konstantareas M, et al. Clomipramine versus haloperidol in the treatment of autistic disorder: a double-blind, placebo-controlled, crossover study. J Clin Psychopharmacol. 2001; 21 (4): 440-444. LMD164483.

The MAH also provided three additional studies conducted in children with autism or pervasive development disorders (Herczeg et al. 1990[60], Sanchez et al. 1995[61], Joshi et al. 1988[62]). These studies were uncontrolled and of short term duration (4 weeks).

Despite the absence of a clear age range and treatment duration across the studies for which haloperidol could be beneficial in this indication, the use of haloperidol in the treatment of symptoms of persistent aggression in children with autism or pervasive developmental disorders has been supported by the HCPOs as an alternative to other treatment options not sufficiently effective or with a safety profile unsuitable for the individual subjects. This allows a wider treatment armamentarium to balance the benefits and risk for several treatment options (FGAs and SGAs).

The SAG clearly indicated that haloperidol is of benefit in this condition for subjects aged 6 years or more not responding to other treatments and that the need for continuation of haloperidol treatment should be re-assessed after 6 weeks.

Taking all relevant clinical data and noting the expert consultations and therapeutic guideline recommendations, the revised indication does not refer to first line treatment and limits the paediatric age range from 6 to 17 years: *'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'.*

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

Tic disorders, including Tourette's syndrome

Two placebo-controlled studies evaluated mean haloperidol doses of 3.5 mg/day in children and adolescents with Tourette syndrome/Tics (Connell et al. 1967[63] and Sallee et al. 1997[64]). Both studies are hampered by a lack of statistical approaches and small sample sizes. The study of Sallee et al. 1997 failed to demonstrate an effect.

Three active-controlled studies were provided. The study of Wu et al. 2009[65] compared a traditional Chinese Medicine treatment with haloperidol in children with Tic disorders, but as a placebo control is lacking, the result of the comparison (no significant difference in effect) cannot be judged. The study of Yoo et al. 2011[66] used haloperidol compared to aripiprazole. Efficacy in a small number of patients could be shown, however, with an unfavourable safety profile of haloperidol leading to a high drop-out (around 35%). The third study was a retrospective review presented by Singer et al. 1986[67], with children aged 2 to 15 years. The data provided in this study do not allow any conclusion on the dose in the different age groups, and patients were highly comorbid (ADHS; approximately 30%).

[60] I Herczeg, S Nagy, & G Bartko. Therapeutic effects of haloperidol in infantile autism. Psychintna Danubiru 2 145-Ix) 1590
[61] Sanchez L E, Adams P B, Uysal S, Hallin A, Campbell M, andSmall A M.'A Comparison of Live and Videotape Ratings: Clomipramine and Haloperidol in Autism'. Psychopharmacology Bulletin 1995: 31(2), 335-338.
[62] Joshi P T, Capozzoli J A., R.N, and J T. Coyle. Low-Dose Neuroleptic Therapy for Children With Childhood-Onset Pervasive Developmental Disorder. March 1988. Am] Psychiatry 145:3,
[63] Connell PH, Corbett JA, Horne DJ, Mathews AM. Drug treatment of adolescent tiqueurs. A double-blind trial of Diazepam and Haloperidol. Br J Psychiatry. 1967;113(497):375-81.
[64] Sallee FR, Nesbitt L, Jackson C. Relative Efficacy of Haloperidol and Pimozide in Children and Adolescents With Tourette's Disorder. Am J Psychiatry. 1997;154:1057-1062.
[65] Wu M, Xiao GH, Yao M et al. Multicenter clinical study on the treatment of children's tic disorder with qufeng zhidong recipe (sic). Chin J Integr Med. 2009; 15 (4): 254-260. LMD268942.
[66] Yoo HK, Lee JS, Paik KW et al. Open-label study comparing the efficacy and tolerability of aripiprazole and haloperidol in the treatment of pediatric tic disorders. Eur Child Adolesc Psychiatry. 2011; 20:127-135. LMD288145.
[67] Singer HS, Gammon K, Quaskey S: Haloperidol, fluphenazine and clonidine in Tourette syndrome: controversies in treatment. Paediatr Neurosci. 1985-1986; 12(2):71-74. LMD53110.

The publications of Shapiro (1989)[68] and Borison (1984)[69] suggested efficacy of haloperidol in Tourette's syndrome, however, both authors did not specify the number of children and adolescents included, since these were mixed studies also including adults.

Therapeutic guidelines are conservative in recommending haloperidol in children with Tic disorders/Tourette`s syndrome due to the fact that adverse drug reactions render haloperidol a "third line treatment" despite its approval in some Member States (Roessner et al., 2011[70]; Guideline on Tic disorders by the German society of child and adolescent psychiatry, S1). According to the European Society for the Study of Tourette syndrome (ESSTS) Guideline, haloperidol is not the preferred option for this condition, in both paediatric and adult patient populations.

Further input was received by SAG experts on the treatment of Tic disorders including Tourette's syndrome in adults as well as in children and adolescents. It was advised by the SAG to retain a revised indication referring to second- to third- line status for oral haloperidol, so that pharmacological treatment of tic disorders, including Tourette syndrome, would be reserved for cases presenting with major limitations/disabilities in subjective, social, emotional and functional domains. In this context, the SAG also expressed the view that treatment with haloperidol should only be considered in patients 10 years and older in whom non-pharmacological and pharmacological treatments have failed. Comments received from the HCPOs support the inclusion of haloperidol as a treatment alternative - a second to third line treatment option.

The CHMP agreed that Haldol can be recommended as an individual treatment option for Tic disorders including Tourette's syndrome, which has a safety profile distinct from atypical neuroleptics. The agreed wording for the Paediatric indication is: *'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'.*

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

Schizophrenia (oral)

Taking into consideration the results from the studies provided by the MAH, other available data including the results from PET imaging studies with haloperidol, doses for the treatment of acute schizophrenia should be indicated to be significantly lower (especially in the first episode of schizophrenia), to avoid adverse drug reactions associated with doses exceeding the EPS threshold dose, as well as D2 receptor up-regulation leading to even higher doses to achieve adequate responses. The maintenance treatment dose should be aligned with this acute dose restriction.

Following the HCPOs experts input, the CHMP agreed on a daily dose of 2 to 10 mg/day; 2 to 4 mg/day for first episode schizophrenia and up to 10 mg/d multi episode schizophrenia. The maximum dosage is 20 mg/day because safety concerns outweigh the clinical benefits of treatment at higher doses. Advice that EPS can occur more often with doses above 10 mg/day has also been included.

Based on clinical experience, the SAG recommendation for the dosage in this indication in the paediatric population is between 0.5 mg and 3 mg/day (with the option to escalate to 5 mg after

[68] Shapiro A, Shapiro E, Eisenkraft GJ et al. Treatment of Gilles de la Tourette svndrome with pimozide. Am J Psychiatry. 1983; 140:1183-1186. LMD33363.
[69] Borison RL, Ang L, Hamilton WJ, Diamond BI, Davis JM. Treatment approaches in Gilles-de-la-Tourette syndrome. Brain Res Bull. 1984; 11 (2): 205-208, LMD39280.
[70] Schlander M, Schwarz O, Rothenberger A, Roessner V Tic disorders: prevalence and co-occurrence with attention-deficit/ hyperactivity disorder in a German community sample. Eur Psychiatry 26 (2011) 370–374.

reassessment), and the treatment duration is dependent on the need in each individual case. This was endorsed by the CHMP.

Delirium (oral and injectable)

Since delirium is in general a short-term condition, it was recommended lowering the dose range, which is still considered in line with most of the positive results, and for which the occurrence of extrapyramidal AEs seems to be limited and acceptable. The wording has been amended reflecting that haloperidol should be started at the lowest possible dose of 1 mg/day and be increased to doses of 10 mg/day. The proposed maximum dose of 10 mg/d in the younger delirium patients is supported by external experts. Literature data in support of titrating haloperidol doses for subjects continuing to be agitated, derive from Practice Guideline for the Treatment of Patients with Delirium (Trzepacz et al. 1999[71]; haloperidol 1 to 2 mg orally to be repeated every two to four hours as needed) and from German scientific literature on psychopharmacology (Benkert and Hippius, 10th edition).

The dose recommendation for the injectable haloperidol formulation is in line with the oral formulation.

Mania associated with bipolar I disorder (oral)

The dosing recommendations have been restricted 2 to 10 mg/day, since the incidence for extrapyramidal symptoms and the risk for developing tardive dyskinesia is higher for patients with affective disorders compared to patients with schizophrenia.

The maximum dosage is 15 mg/day. However to ensure the appropriate management of patients being treated for conditions in which there is a risk of switch to depression, the MAH has proposed wording in Section 4.2 of the SmPCs to alert prescribers to evaluate the continuation of Haldol use early in treatment, with a cross reference to section 4.4.

Psychomotor agitation associated with psychotic or bipolar disorder (oral and injectable)

The dose recommendations proposed by the MAH for intramuscular haloperidol (5-15 mg/day), and for oral administration (5-10 mg/day) were considered to be acceptable. The proposed maximal daily dose is 20 mg/day for oral and injectable administration.

Wording regarding the dosage relating to the transfer of patients to the oral formulation after achieving control over severe symptomatology with intramuscular haloperidol, in the indication psychomotor agitation associated with psychotic disorder or manic episode has also been included.

Psychotic symptoms, suspiciousness, hostility and impulsive behaviour associated with borderline and schizotypal personality disturbances (oral)

This indication was not agreed and therefore a dose recommendation was not discussed.

Agitation, aggression and psychotic symptoms associated with dementia (for up to 12 weeks) (oral)

Taking into account the SAG's view based on clinical experience, a dose range between 0.5 and 5mg/day was agreed. A reassessment of the need to continue treatment with Haloperidol after 6 weeks has been recommended.

Tic disorders, including Tourette's syndrome (oral)

Taking into account the SAG's view based on clinical experience, the dose recommendation was agreed to be in the range of 0.5 to 5 mg/day for adults. Within this range, the treatment should be maintained

[71] Trzepacz P, Breitbart W, Franklin J, Levenson J, Martini D. R, Wang P, H. (Consultant). Practice Guideline for the treatment of patients with delirium. American Psychiatric Association. 1999.

at the lowest effective dose. Periodic stopping for the reassessment of the need to continue the treatment should be performed every 6 or 12 months.

Choreatic movement disorders, including Huntington's disease (oral and injectable)

The dose recommendations proposed by the MAH for oral administration is 2-10 mg/day and for intramuscular haloperidol it is 2-5 mg/day and for. The proposed maximum daily dose is 10 mg/day for the injectable administration.

As an adjunct to benzodiazepines in the treatment of delirium, delusions or hallucinations in alcohol withdrawal syndrome (IV)

This indication was not agreed and therefore a dose recommendation was not discussed.

Agitation in acute alcohol intoxication (injectable)

This indication was not agreed and therefore a dose recommendation was not discussed.

Postoperative nausea and vomiting - PONV (injectable)

Most of the reviewed studies used haloperidol at doses of either 1 or 2 mg. Therefore the dose recommendations proposed by the MAH for intramuscular haloperidol in both the prophylaxis and treatment of PONV is 1-2 mg.

Paediatric population

Bearing in mind that that Haloperidol is not to be considered a first line treatment for schizophrenia in paediatric patients aged 13 to 17 years, but rather a 3rd line treatment or a 2nd line treatment, the SAG recommends that for this indication, the dose is between 0.5 mg and 3 mg/day, with the option to escalate to a maximum dose of 5 mg/day after reassessment. The SAG was also of the view that the treatment duration is dependent on the need in each individual case. The CHMP endorsed the SAG's proposals.

Regarding the treatment of 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, the SAG expressed the view that the dose should be in the range of 0.5 to 3 mg/day for children and adolescents. Within this range, the treatment should be maintained at the lowest effective dose. Periodic stopping for the reassessment of the need to continue the treatment should be performed every 6 or 12 months.

For the treatment of persistent, severe aggression in children and adolescents with autism or pervasive developmental disorders, when other (non-) pharmacological treatments have failed or are not tolerated, the recommended dosages are: 0.5 to 3 mg/day in children aged 6 to 11 years and 0.5 to 5 mg/day in adolescents aged 12 to 17 years, administered orally in divided doses (2 to 3 times a day). The need for treatment continuation should be reassessed after 6 weeks.

Elderly population

Pharmacokinetic investigations found higher serum concentrations of haloperidol in the elderly compared to younger subjects. Elderly patients are especially sensitive to adverse effects of antipsychotic drugs (sedation, EPS, tardive dyskinesia, anticholinergic adverse events and orthostatic dysfunction). Therefore, starting with the lowest possible dose with gradual upward dose titration is recommended.

Dose recommendations in the elderly for treatment of dementia-related symptoms have been adapted to start with 0.5 mg/day; for all other indications half the lowest adult dose is recommended. Careful and gradual dose titration in the elderly is recommended. The maximum dosage is 5 mg/day. However it has also been addressed that some elderly patients may tolerate higher haloperidol doses due to long-standing schizophrenia already starting in adulthood. In such cases re-assessment of the patient's individual benefit/risk profile is recommended.

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. The wording in this subsection was hence revised to include the information that patients with severe renal impairment may require lower starting dose and gradual dose adjustment, with a cross reference to section 5.2.

Hepatic impairment

No studies were retrieved examining the pharmacokinetics of haloperidol 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, adjusted according to the patients' need, with a cross reference to section 5.2.

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 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.Furthermore, 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 has also included 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 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 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 in such a condition 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 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 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 decreased bone mineral density and osteoporosis in sections 4.4 and 4.8 of the SmPC.

Switch from mania to depression

The risk of a rapid switch to depression in patient populations with bipolar disorder has been reflected under a separate subheading. Close supervision of patients and in particular those at high risk, especially in early treatment and the need to monitor for any clinical worsening, suicidal behaviour or thoughts and unusual changes in behaviour by patients and/or caregivers has been included.

Paediatric population

Although limited long-term safety data are available, review of the existing safety data of oral haloperidol in the paediatric population indicate a risk of developing extrapyramidal symptoms, including tardive dyskinesia, and sedation. The wording for the warning on response and withdrawal has been revised in line with the wording of other antipsychotic medicinal products.

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. 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 have 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 guidelines.

Pregnancy

An adequate 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 drug 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 gonadonal 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 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 frequency category for the postmarketing adverse drug reactions was assigned based on the incidence in haloperidol clinical trials or epidemiology studies, as stated in the Guideline on SmPC (September 2009).

Further explanation on how frequencies were calculated for the following ADRs: somnolence, liver function test abnormal, and hyperhidrosis was provided by the MAH. The preferred term (PT) Hepatitis Cholestatic is covered by the broader PT Hepatitis that is already listed adverse drug reaction for haloperidol. Although there are several mechanisms that could cause angioedema, the reported cases were considered sufficient to list angioedema (of not known frequency) in section 4.8 of harmonized SmPC for Haldol.

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.

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.

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 dosages.

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 submit any evidence that haloperidol causes or aggravates anhedonia, and therefore no additional wording to the SmPC was suggested as there is a lack of proof of causality.

Additional wording has been included on the site of administration of injectable haloperidol in the treatment and prophylaxis of nausea and vomiting.

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

Absorption

The wording proposed by the MAH referring to the pertinent literature of Cheng et al. (1987)[72] and Forsman et al. (1976)[73] for the oral formulation, and Schaffer et al. (1982)[74] for the intramuscular formulation was considered to be acceptable.

The bioavailability of haloperidol after administration of oral solution formulations was in the same range as after administration of the tablet formulations. The mean bioavailability values range from 60% to 70%. Inter-individual variability has also been supported by clinical data.

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)[75] 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

Significant inter-individual variability in elimination half-life and clearance has been reported. Mean elimination half-life after oral haloperidol intake has been found to range from 14.5 h (Holley et al., 1983[76]) to 36.7 h (Midha et al., 1989[77]). The range of the mean elimination half-lives has therefore been revised to 15-37 hours.

After intramuscular injection of haloperidol, mean elimination half-life was found to be on average 24 hours with a range of 12.8 to 35.5 hours (Cressman et al, 1974[78]).

Excretion of haloperidol in the faeces was approximately 20% after IV administration and increased to approximately 30% after oral administration.

[72] Cheng YF, Paalzow LK, Bondesson U, et al. Pharmacokinetics of haloperidol in psychotic patients.Psychopharmacol. 1987;91(4):410-414.
[73] Forsman A, Öhman R. On the pharmacokinetics of haloperidol. Nord Psyk Tidsskr. 1974;28:441-448.
[74] Schaffer CB, Shahid A, Javaid JI, Dysken MW, Davis JM. Bioavailability of intramuscular versus oral haloperidol in schizophrenic patients. J Clin Psychopharmacol. 1982;2(4):274-277.
[75] 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.
[76] Holley F O, Maglioni J R,. Stanski D R, Lombrozo L, and Hollister L E. Haloperidol kinetics after oral and intravenous doses. Clin. Pharmacol. Thcr. April 1983. 477-484
[77] Midha K K, Chakraborty B S, Ganes D A., Hawes E M, Hubbard J W, Keegan D.L., Korchinski E D and McKay G. Intersubject Variation in the Pharmacokinetics of HaloDeridol and Reduced HaloDeridol. J Clin Psychopharmacol. 1989. 9(2), 98-104.
[78] Cressman W A., Bianchine J R., Slotnick V. B., Johnson P. C., Plostnieks J. Plasma level profile of Haloperidol in man following intramuscular administration. Eur. J. Clin. Pharmacol. 7, 99-103 (1974).

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

Linearity / non-linearity

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

However, a linear relationship of oral haloperidol dose and concentration has not unequivocally been shown for the paediatric population. There are limited data to support a definite conclusion on a dose-concentration relationship in the paediatric population. The MAH cited the study of Singer (1982)[79] to support that there is an increase in concentration with dose increases. The raw data however do not point towards a linear relationship, similar to the study reported by Morselli (1979)[80]. The SmPC has been revised accordingly.

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.[81]). In a study evaluating plasma concentrations of haloperidol and reduced haloperidol in elderly and adult patients (Chang 1996[82]), the metabolic ratios of reduced haloperidol to haloperidol were about twice as high in the elderly vs. the adult patients. Dosage 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. 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 precautionary statement for patients with hepatic impairment (half of the initial dose for the injectable formulation, and dose adjustments for the oral formulation) as mentioned in section 4.4.

Paediatric population

Information on the paediatric response from two studies in children receiving haloperidol treatment for tics and Tourette's syndrome has been included in this subsection for the oral formulation.

[79] Singer HS, Tune LE, Butler IJ, Zaczek R, Coyle JT. Clinical symptomatology, CSF neurotransmitter metabolites, and serum haloperidol levels in Tourette syndrome. Adv Neurol. 1982;35:177-183.
[80] Morselli PL, Bianchetti G, Durand G, Le Heuzey MF, Zarafian E, Dugas M. Haloperidol plasma level monitoring in pediatric patients. Ther Drug Monit. 1979;1(1):35-46.
[81] 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.
[82] 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.

Pharmacokinetic/pharmacodynamics relationships

Cardiovascular Effects

The wording proposed by the MAH regarding the risk of 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)[83], Van Putten et al. (1992)[84], Volavka et al. (1992[85], 1996[86]), Jibiki et al. (1993)[87], and Kapur et al. (1997)[88]. Further supporting data derive from Fitzgerald (2000)[89], Nyberg (1995)[90] and Panagiotidis (2007)[91]. This therapeutic concentration range is in line with the AGNP Consensus Guidelines (2011), where it is stated to be 1 to 10 ng/ml. With regard to the proposal of a decreased treatment dose for schizophrenia, a therapeutic range of 1 to 10 ng/ml is supported based on study data and pertinent Therapeutic Drug Monitoring (TDM) guidance (AGNP Consensus Guidelines (2011)).

The therapeutic effect of antipsychotics and safety 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 the therapeutic effect, without an increased incidence of adverse events, including EPS (Gieglin 2010[92]; Kapur 2000[93]). 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 the section 5.2 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 confirmed in humans. This has been adequately reflected in this section.

[83] 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.
[84] 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.
[85] Volavka J, Cooper TB, Czobor P, et al. Haloperidol blood levels and clinical effects. Arch Gen Psychiatry. 1992;49(5):354-361.
[86] 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.
[87] 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.
[88] 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.
[89] Fitzgerald CH. A double-blind comparison of haloperidol with perphenazine in acute psychiatric episodes. Current Therapeutic Research 1969;11(8):515–519.
[90] 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.
[91] 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.
[92] 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.
[93] 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. /Km J Psychiatry 157:4, April 2000

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

A SAG and HCPOs consultation 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 of the CHMP, and are reflected in the relevant sections above. The final agreed indications can be found in the recommendation section below.

4. Recommendation

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 formulation:

- 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 formulation:

- 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 formulation 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.

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 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).