EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

13 December 2012
EMA/177796/2013
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Fanaptum

International non-proprietary name: **iloperidone**

Procedure No. **EMEA/H/C/002371/0000**

Note

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

7 Westferry Circus ● Canary Wharf ● London E14 4HB ● United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7523 7455
E-mail info@ema.europa.eu **Website** www.ema.europa.eu

Table of contents

List of abbreviations

5-HT	5-hydroxytryptamine
8-OH-DPAT	8-hydroxy-2 (di-n-propylamino) tetralin
ADME	absorption, distribution, metabolism, and excretion
AE	adverse event
ANCOVA	analysis of covariance
APD	Action potential duration
$AUC_{0-\infty}$	area under the plasma concentration –time curve from time zero to infinity [amount x time x volume^{-1}]
BID	bis in die = twice daily
Bpm	Beats per minute
BPRS	PANSS-derived Brief Psychiatric Rating Scale
CNS	Central nervous system
CNTF	ciliary neurotrophic factor
CYP	cytochrome P450
EAD	Early after-depolarisation
ECG	Electrocardiogram
EPS	Extrapyramidal symptoms
ESRS	extrapyramidal symptom rating scale
FS63Ter	frame shift mutation that results in a termination codon at position 63
GBL	Gamma-butyrolactone
HAL	haloperidol
HERG	Human ether à-go-go-related gene
HMR	Hoechst-Marion-Roussel
ILO	iloperidone
ILO-oet	Iloperidone over-encapsulated tablets
i.p.	intraperitoneal
ISS	Integrated Summary of Safety
ITT	Intent to Treat
L-DOPA	L-dihydroxyphenylalanine
LOCF	last observation carried forward
MMRM	mixed model repeated measures
MPE	Main Photo Effect
MTD	Maximum Tolerable Dose
NOAEL	No-Observed-Adverse-Effect Level
NOEL	No-Observed-Effect Level
PANSS	Positive and Negative Syndrome Scale
PIF	Photo-irritation factor
PM	Poor metabolizer
QD	qua que die (Latin: once daily)
QT	QT interval of the ECG waveform
QTcF	Fridericia correction of QT duration
RIS	risperidone
SD rat	Sprague-Dawley rat
SNC	Substantia nigra pars compacta
SOC	System Order Class
SUD	Sudden Unexpected Death
t½	half life of drug elimination
t_{max}	time-to-peak concentration
TdP	Torsade de pointes
TTC	Theshold of toxicological concern
V_{ss}	Volume of distribution at steady-state
VTA	Ventral tegmental area
ZIP	ziprasidone

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Vanda Pharmaceuticals Limited submitted on 26 June 2011 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Fanaptum through the centralised procedure under Article 3(2)a of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 24 June 2010.

The applicant applied for the following indication treatment of schizophrenia in adults.

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application.

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain tests or studies.

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/71/2011 on the granting of a product-specific waiver for all subsets of the paediatric population for iloperidone in the treatment of schizophrenia by the PDCO.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

New active Substance status

The applicant requested the active substance iloperidone contained in the above medicinal product to be considered as a new active substance in itself, as the applicant claims that it is not a constituent of a product previously authorised within the Union.

Scientific Advice / Protocol Assistance

The applicant received Scientific Advice from the CHMP on 25 March 1999 and on 21 September 2001. During the development of iloperidone, scientific advice has been obtained by the CPMP relating to clinical issues on 25th March 1999 (CPMP/775/99) and on 21st September 2000 (CPMP/2366/00) with regard to the carcinogenic potential of the iloperidone metabolite P95, the intended toxicological and clinical phase III program. Moreover, scientific advice was given by the national competent authorities of Sweden, Denmark, The United Kingdom, The Netherlands and France in May and June 2001.

Licensing status

Fanaptum has been given a Marketing Authorisation in the United States of America on 06 May 2009 and in Israel on 06 August 2012.

A new application was filed in the following countries: Argentina, Mexico

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP and the evaluation teams were:

Rapporteur: **Martina Weise**

Co-Rapporteur: **Kristina Dunder**

- The application was received by the EMA on 27 June 2011
- The procedure started on 20 July 2011
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 7 October 2011. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 10 October 2011.
- During the meeting in November 2011, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 18 November 2011.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 14 May 2012.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 29 June 2012.
- During the CHMP meeting on 19 July 2012, the CHMP agreed on a list of outstanding issues to be addressed in writing and by the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 11 October 2012.
- During the CHMP meeting in November 2012, outstanding issues were addressed by the applicant during an oral explanation before the CHMP. The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the list of outstanding issues on 29 November 2012 .
- During the meeting on 10-13 December 2012, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a negative opinion.

2. Scientific discussion

2.1. Introduction

This application for marketing authorisation concerns iloperidone for the treatment of schizophrenia in adults. Iloperidone is a piperidinyl-benzisoxazole derivative with antagonistic activity at serotonergic 5-HT2A, dopaminergic D2/D3 and adrenergic receptors.

The Applicant claims that the antipsychotic activity will be connected with reduced liability for extrapyramidal symptoms (especially akathisia), prolactin elevation, sedation, and weight gain as compared to currently marketed antipsychotic medications in the European Union (EU).

The clinical development of iloperidone was initiated by Hoechst Marion Roussel (HMR) in 1990. Novartis Pharmaceuticals Corporation/Novartis Pharma AG (Novartis) licensed iloperidone in 1998 and continued its clinical development program. In 2004, Vanda Pharmaceuticals Inc. (Vanda), licensed iloperidone and continued its clinical development program. Studies by all 3 sponsors are included in this submission.

In May 2009 iloperidone tablets (fanapt) have been approved for the treatment of schizophrenia in adults by FDA. Due to QT-prolonging ability the product has been licensed as second line treatment. The target dose recommended in the SPC is 6-12 mg twice daily.

2.2. Quality aspects

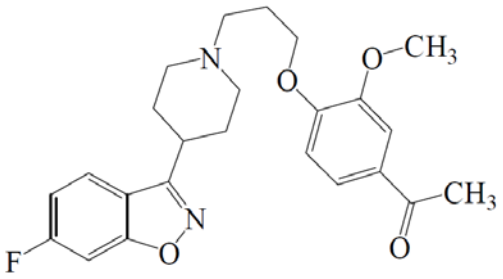
2.2.1. Introduction

The finished product is presented as tablet containing 1 mg, 2 mg, 4 mg, 6 mg, 8 mg, 10 mg and 12 mg of iloperidone as the active substance. The other ingredients are lactose monohydrate, microcrystalline cellulose, hypromellose, crospovidone, silica and magnesium stearate.

The proposed packaging for the finished tablets consists of PA/Alu/PVC blisters and HDPE bottles closed with child resistant polypropylene caps. The HDPE bottles contain desiccant (Silica gel in the HDPE canister).

2.2.2. Active Substance

Iloperidone is a white to off-white crystalline powder, not hygroscopic and soluble in organic solvents such as acetonitrile and methanol, moderately soluble in acidic aqueous solutions and sparingly soluble in basic aqueous solutions. The chemical name is 1-[4-[3-[4-(6-Fluorobenzo[d]isoxazol-3-yl)-1-piperidinyl]propoxy]-3-methoxyphenyl]ethanone 4'-[3-[4-(6-Fluoro-1,2-benzisoxazol-3 yl) piperidino]propoxy]-3'-methoxyacetophenone. The molecular formula is $C_{24}H_{27}FN_2O_4$ and has the following chemical structure:



Iloperidone has no chiral carbon atoms. Iloperidone has been observed only in a single polymorphic state and which has been confirmed by XRPD. No amorphous form of iloperidone has been observed during the drug development.

Manufacture

Iloperidone is synthesised in eight main steps using commercially available and well defined starting materials. The synthesis consists of a two branch synthesis to form the two final intermediates which are condensed in the last step followed by a micronisation step. The final active substance is purified by crystallisation. All critical steps have been identified and discussed. The manufacturing process is well described.

Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented.

A comprehensive discussion on impurities and residual solvents was presented and the results were well within the limits set by the ICH guidelines Q3A and Q3C.

Batch analysis data are provided on three batches produced by the proposed synthetic route, and the batch analysis data show that the active ingredient can be manufactured reproducibly.

The purified active substance is packed in double low-density polyethylene (LDPE) plastic liners with anti-static additive. The plastic liners are sealed with red polyamide ties and placed inside a round fibreboard drum with a black high-density polyethylene (HDPE) lid. The lid is sealed with a tamper-evident metal, clamp ring fitted with a numbered security seal.

Specification

The active substance specification includes tests for: appearance, identification (FT- IR), melting point, purity, loss on drying, impurities (HPLC), residual solvents (GC), heavy metals, assay (HPLC & pontentiometric titration, 98.0– 102.0%), particle size, polymorphism (XRD), loss on drying (Ph.Eur.), sulphate ash (Ph.Eur.), appearance of solution, colour of solution (Ph.Eur.), microbiology limit test (Ph.Eur.).

A detailed description for all analytical methods was provided. Full method validation data was also provided for the in-house analytical methods in accordance with the relevant ICH Guidelines. The analytical methods proposed are suitable to control the quality of the active substance. The impurity limits are acceptable and there is no concern from the point of view of safety.

Batch analysis data on four development batches, nine early development pilot batches, seventeen pilot batches and three commercial batches of the active substance are provided. All results are within the specifications and consistent from batch to batch.

Stability

Six production scale batches and three pilot scale batches of the active substance packed in the intended commercial packaging (LDPE bags) from the proposed manufacturers were put on stability testing as per ICH conditions: under long term (25°C/60%RH) for up 24 months, and accelerated (40°C/75%RH) for up 6 months. Additionally, only three production scales were tested at 30°C/60%RH and -20°C for 60 months.

The active substance used in the primary stability studies was manufactured according to the commercial process. The following parameters were tested: appearance, identification (FT- IR & XROD), melting point, loss on drying (Ph.Eur.), appearance of solution, colour of solution (Ph.Eur.), impurities (HPLC), assay (HPLC - 98.0– 102.0%) and microbiology limit test (Ph.Eur.).

Forced degradation studies were conducted by exposing the active substance to high temperature, acid, base, oxidative and high intensity light conditions. It was only noted minor degradation of the active substance.

Photostability testing following ICH guidelines Q1B was performed on one batch per manufacture of the active substance. The results showed discoloration of the active substance.

The stability results indicate that the active substance is sufficiently stable at controlled room temperature and protected from light. The results justify the proposed retest period in the proposed container.

2.2.3. Finished Medicinal Product

Pharmaceutical Development

Iloperidone tablets have been developed as immediate released tablets (1 mg, 2 mg, 4 mg, 6 mg, 8 mg, 10 mg and 12 mg).
The first Iloperidone drug product formulation included 1 mg, 2 mg, 4 mg, 5 mg, 10 mg and 25 mg capsules using excipients (corn starch, lactose, pregelatinised starch, croscarmellose sodium, purified water) and processes which are also suitable for use in compressed tablets. In addition, a film-coated tablet formulation was developed for the 1 mg strength. The first formulation for the film-coated tablet was essentially the same as that for the capsules except that the powder blend was granulated using water, dried, blended and then compressed into tablets followed by film coating. Based on these experimental studies more film-coated tablets strengths were developed (2 mg, 3 mg, 4 mg, 6 mg and 8 mg).

In a second part of the pharmaceutical development the tablet formulation was refined in order to obtain tablets without film coating and to develop new strengths. An over-encapsulated tablet was employed for the drug product for use in clinical studies. The tablets, which were subsequently over-encapsulated, used the same formulation as already described with the exception of the film-coating. The over-encapsulated tablets were developed in the following strengths: 1 mg, 2 mg, 4 mg, 6 mg, and 8mg. Subsequently new strengths of 10 mg and 12 mg were also developed. The tablet formulations were then further optimised by using different excipients resulting in the new final commercial tablet formulation (lactose monohydrate, microcrystalline cellulose, hypromellose, purified water, crospovidone, silica and magnesium stearate). A bioequivalence study was performed using the 1 mg overcapsulated tablets and the tablets not overcapsuled. The results of the study showed that the two formulations were bioequivalent. The primary packaging proposed is adequately described (PA/Alu/PVC blisters and HDPE bottles closed with child resistant polypropylene caps). The packaging materials comply with Ph.Eur. requirements and are adequate to support the stability and use of the product.

Adventitious agents

It is confirmed that the lactose is produced from milk from healthy animals in the same condition as those used to collect milk for human consumption and that the lactose has been prepared without the use of ruminant material other than calf rennet according to the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents Via Human and veterinary medicinal products

Manufacture of the product

The manufacturing process consists of seven main steps: pre-blending, wet granulation, fluid-bed drying, milling, final blending, compression and packaging. The process is considered to be a standard manufacturing process.

The manufacturing process has been validated by a number of studies for the major steps of the manufacturing process and it is able to consistently produce a finished product of the intended quality. The in-process controls are adequate for this pharmaceutical form.
The batch analysis data on three batches per strength show that the tablets can be manufactured reproducibly according to the agreed finished product specification, which is suitable for control of this oral preparation.

Product specification

The finished product release specification includes appropriate tests for appearance (visual), identification (HPLC), hardness, dissolution (HPLC), disintegration, mean mass, content of uniformity (HPLC), loss on drying, mass uniformity, assay (HPLC - 95.0%-105.0%), impurities (HPLC) and microbial limit test (Ph.Eur).

Batch analysis results in three commercial batches per strength confirm consistency and uniformity of manufacture and indicate that the process is under control.

Stability of the product

Stability data of three batches of each strength stored under long term conditions for 36 months at 25ºC/60%RH and for up to 6 months under accelerated conditions at 40ºC/75%RH according to ICH guidelines were provided. The batches of medicinal product are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.

The stability samples were tested for appearance, dissolution, disintegration, content uniformity, loss on drying, microbial limit test (Ph.Eur.), assay (HPLC - 95.0%-105.0%), impurities (HPLC), friability and hardness.

In addition, the photostability of one batch of each strength was evaluated in accordance with ICH guideline Q1B (Photostability Testing of New Drug Substances and Products). The results showed changes in the appearance, decrease of assay and in increase in the impurities content in the tablets exposed outside of the container closure system. No changes were observed in the tablets stored in the proposed packaging.
The proposed shelf-life of 48 months with the labelled storage condition “Store in the original package in order to protect from moisture and light” has been justified by stability data provided.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The potential impurities, by products of the synthesis and degradation products, have been discussed in detail. The control test and specifications for the active substance have been adequately established. There are no novel excipients used in tablet formulation and all excipients are compendial, which are controlled to the requirements of the current Ph.Eur. monographs. The manufacturing process of these tablets was considered to be a standard manufacturing process. The results of tests carried out indicate consistency and uniformity of important product quality characteristics and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in the clinic.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

Based on the data provided the quality of this medicinal product is considered to be acceptable. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.2.6. Recommendation(s) for future quality development

None.

2.3. Non-clinical aspects

2.3.1. Introduction

This application concerns the new active substance iloperidone for the treatment of schizophrenia in adults. Iloperidone is a piperidinyl-benzisoxazole derivative with antagonistic activity at serotonergic 5-HT_{2A}, dopaminergic D_2/D_3 and adrenergic receptors.

Iloperidone has been formulated as tablets of 1, 2, 4, 6, 8, 10 or 12 mg each. The recommended starting dose is 1 mg b.i.d, which must be slowly titrated to the target dose range of 6-12 mg b.i.d. to avoid orthostatic hypotension due to the α-adrenergic inhibitory activity of the compound.

The preclinical development of iloperidone was mainly performed by Novartis and more recently continued by the Applicant, Vanda Pharmaceuticals Ltd.

During the development of iloperidone, scientific advice has been obtained by the CPMP relating to clinical issues and with regard to the carcinogenic potential of the iloperidone metabolite P95, the intended toxicological and clinical phase III program.

All pivotal safety pharmacology and toxicology studies were conducted in compliance with GLP.

2.3.2. Pharmacology

Iloperidone is a piperidinyl-benzisoxazole derivative (1-[4-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl] propoxy]-3-methoxyphenyl] ethanone). Similar to the receptor interaction profiles known from other members of the class of atypical antipsychotic agents, iloperidone binds with high antagonistic affinity to serotonin 5-HT_{1A}, 5-HT_{2A} and dopamine D_2 and D_3 receptors and moderately interacts with dopamine D_4, serotonin 5-HT_6 and 5-HT_7 and adrenergic α1 and α2 receptors. The higher affinity for 5-HT_{2A} compared to D_2 receptors suggests a reduced liability to evoke EPS. In contrast, iloperidone has low affinity for other serotonin, dopamine D_1 and histamine H1 receptors and does not reveal any relevant interaction with muscarinic acetylcholine receptors or the glycine-binding site of N-methyl-D-aspartate (NMDA) receptors. The binding of iloperidone to adrenergic α_1 and α_2 receptors might account for its potential to cause orthostatic hypotension and vasodilatation, which have been detected in rats and dogs.

Pharmacological evaluation of the iloperidone metabolites P88 and P89 revealed similar antagonistic activities at serotonergic, adrenergic and dopaminergic receptors, with comparable potencies between P89 and the parent compound. P88 showed weaker affinity to these sites. P95 also exerted similar antagonism at serotonergic and adrenergic receptors, but lower activity towards dopamine receptors.

As seen with other antipsychotic drugs, iloperidone and P88, but not P95, showed prominent blockade of human-ether-a-go-go-related gene (HERG) currents demonstrating stronger interaction than ziprasidone (IC_{50} 30-40 nM vs. $\approx$ 50-80 nM). In agreement with these findings, iloperidone and its metabolite P88 concentration-dependently prolonged action potential duration in dog Purkinje fibres showing the characteristic profile of a pure K^+ channel blocking agent. At highest test concentrations, even triangulations but no early after-depolarisation (EAD) were detected. Interestingly, no ECG changes were noted in various studies in dogs. However in an ICH E14 guideline conform clinical thorough QT study, pronounced QT prolongations were noticed at therapeutic iloperidone doses, which resulted in the presence of CYP2D6 or 3A4 inhibitors in only 3.75- or 6-fold lower exposure levels than the IC_{50} of iloperidone at the HERG channel. The lack of a safety margin towards therapeutic concentrations in combination with incidences of sudden death related to cardiac events in clinical trials and post-marketing in the USA is alarming and is further addressed clinically (see clinical MO).

No relevant safety pharmacological effects were observed on the respiratory system or the CNS.

Neither iloperidone, nor P95 and P88 exert a significant potential to induce CYP P450 enzymatic activities, but reveal a clinically relevant inhibitory potential for CYP2D6 and CYP3A4/5.

Primary pharmacodynamic studies

2.3.3. In vitro receptor binding profile of iloperidone

Antagonism at dopamine D2 receptors in the mesolimbic/mesocortical system has been the primary target for antipsychotic treatment of schizophrenia, but needs to be balanced by concomitant blockade of 5-HT_2 receptors to reduce liability for the development of extrapyramidal symptoms (EPS) and tardive dyskinesia. For this reason, it was essential to determine the affinity ratio of dopamine vs. serotonin receptor selectivity for iloperidone, which was investigated *in vitro* in several radioligand-binding assays using rat, guinea pig and bovine tissues or CHO, BHK, HEK293 and Sf9 cells stably expressing various dopaminergic and serotonergic receptors. In part, established antipsychotic agents were included for comparison. In addition, the binding profile was complemented based on logarithmic calculation of *in vitro* dissociation (pK_D) or inhibitory constants [pK_i].

Iloperidone exhibited high affinity for human, rat, or bovine dopamine receptors (D_2, D_3, and D_4) and serotonin 5-HT_2 receptors, a profile known from other atypical antipsychotic compounds. Iloperidone also effectively interacted with serotonin 5-HT_{1A} and 5-HT_{1B}, 5-HT_6, 5-HT_7 and sigma receptors, while it demonstrated low affinity for dopamine D_1, D_5 and serotonin 5-HT_3 receptors.

Additional high affinity of iloperidone was apparent at rat and human α1-adrenergic receptors, whereas moderate binding to α_2 receptors was found. In aortic ring preparations, the affinity of iloperidone for vascular α_1-receptors was similar to risperidone (binding constant K_B = 0.5 nM vs. 0.3 nM each) and approximately 13-fold higher compared to clozapine (K_B = 6.8 nM).

Weak interactions were determined with human histamine receptors and very weak affinity was observed at the cholecystokinin B (CCKB gastrin) receptor, the norepinephrine (NE) transporter and guinea pig β1- and β2-adrenergic receptor sites. There was no apparent reactivity at muscarinic receptors, rat NMDA glycine or channel sites or any other receptors tested up to concentrations of 10 µM.

Unlike the typical antipsychotic haloperidol, but similar to the atypical substances clozapine and olanzapine, the affinity of iloperidone for 5-HT_2 receptors was greater than for D_2 receptors, which was confirmed *ex vivo*, when iloperidone effectively competed with spiperone for binding to 5-HT_2 and receptors. This indicates potent antipsychotic action at lower propensity for EPS development.

2.3.4. In vitro receptor binding profile of iloperidone metabolites

The receptor binding characteristics of the three major iloperidone metabolites P88, P89 and P95 were analysed separately in preparations from mice, rats, guinea pigs, monkeys and humans.

Similar to iloperidone, the metabolite P89 was found to bind with high affinity to 5-HT_2 and D_2 receptors, whereas P88 showed about 30-fold and 10-fold weaker activity at each of these sites. Both metabolites also exhibited affinity for 5-HT_{1A}, α_1- and α_2-adrenergic and sigma opiate receptors. Like the parent compound, P88 did not bind to muscarinic receptors (P89 was not tested for interaction).

The metabolite P95 also demonstrated comparable affinity to iloperidone for 5-HT_{2A} and the adrenergic receptors, but exhibited substantially lower binding to dopaminergic D_1, D_2, and D_3 receptors. As P95 does not cross the blood-brain-barrier, it primarily exerts its activity at peripherally located receptors. As seen for iloperidone, P95 did not bind to histamine H_1 receptors.

2.3.5. Antagonistic properties of iloperidone and its metabolites at dopamine, serotonin and adrenaline receptors in vitro and ex vivo

As a compensatory feedback reaction to D_2 receptor antagonism, antipsychotic agents increase dopamine production by increasing activity of tyrosine hydroxylase, which catalyzes the synthesis of the dopamine precursor L-dihydroxyphenylalanine (L-DOPA) from L-tyrosine. L-DOPA is then transformed to dopamine by aromatic L-amino acid decarboxylase.

In agreement with this mechanism, single i.p. injections of 0.3 to 10 mg/kg iloperidone elevated L-DOPA levels in the striatum and nucleus accumbens of rats if the decarboxylation reaction from L-DOPA to dopamine was concomitantly inhibited with 100 mg/kg i.p. NSD-1015. The iloperidone metabolites P88 and P89 also significantly increased L-DOPA accumulation in these regions at 10 and 30 mg/kg i.p. (P88) and 0.03 to 30 mg/kg i.p. (P89), respectively. The typical antipsychotic compound haloperidol revealed comparable potency, whereas the atypical agent clozapine was a minor dopamine receptor antagonist.

Likewise, the release of norepinephrine is stimulated by α2-receptor antagonists and inhibited by α2-agonists in a negative feedback loop. Iloperidone was found to enhance norepinephrine release on rat cortical slices, hence indicating α2-antagonist properties.

In addition, iloperidone was a moderately potent inhibitor of serotonin uptake and about 10-fold weaker inhibitor of norepinephrine uptake in synaptosomal preparations from whole rat brain as well as of dopamine uptake in synaptosomes from rat striatum.

These antagonistic effects were further elucidated using HEK293, CHO K1 or HeLa expressing human D_2- and D_3-, 5-HT_{1A} and 5-HT_6 and adrenaline α_{2A}- and α_{2C}-receptors, respectively. Following stimulation by the cAMP inducer forskolin, cAMP levels were down-regulated by dopamine, norepinephrine or the serotonin agonist 8-hydroxy-2 (di-n-propylamino) tetralin (8-OH-DPAT). Iloperidone failed to reduce accumulation of cAMP, but surmounted the agonistic effects of the neurotransmitters.

Furthermore, the metabolite P88 and its enantiomer R(+)-P88 inhibited the cAMP reduction induced by agonists against α_{2C}-adrenergic and D_2-dopaminergic receptors with similar affinity than the parent compound. Thus, iloperidone and its metabolite P88 show comparable antagonistic activities at dopamine, serotonin and adrenaline receptors.

2.3.6. Antagonism of iloperidone and its metabolites on dopamine receptors in vivo

The inhibition of dopamine receptors in the substantia nigra pars compacta (SNC) of the brain is hypothesised to be important for efficacy of antipsychotic drugs, whereas blockade of dopaminergic neurons in the ventral tegmental area (VTA) has been associated with EPS liability. In order to differentiate between activities of iloperidone on both neuronal populations *in vivo*, the substance was administered either one time or once daily for 21 days before neuronal harvesting. At the time of sampling, neurons were identified by their electrophysiological characteristics in the SNC and VTA regions of the midbrain.

Single administration of either iloperidone (5 mg/kg i.p.), haloperidol (0.5 mg/kg i.p.), or clozapine (20 mg/kg i.p.) resulted in significant increases in the number of spontaneously active dopaminergic neurons in both the SNC and VTA areas, whereas lower doses of iloperidone (1 and 2 mg/kg i.p.) resulted in a significant increase in the SNC area only. Single doses of the iloperidone metabolites P88 (0.25 or 0.5 mg/kg i.p.) or P89 (0.5 mg/kg i.p.) similarly increased the number of spontaneously active dopaminergic neurons in the VTA and the SNC.

Following repetitive dosing for 21 days, iloperidone (5 and 10 mg/kg i.p.), its metabolite P89 (0.5 or 5 mg/kg i.p.) and clozapine (20 mg/kg i.p.) significantly decreased neuronal activity in the VTA, whereas increases were noted in the SNC. In contrast, haloperidol (0.5 mg/kg) significantly decreased dopaminergic action in both areas. These decreases of dopamine neuronal activity might be explained by a block of depolarisation. The selectivity seen with iloperidone and clozapine in the VTA points towards antipsychotic efficacy of these agents at reduced EPS propensity compared with the typical antipsychotic haloperidol.

Another study investigated the effect of iloperidone, clozapine, and haloperidol on suppression of single dopamine neuron-firing rates in the SNC induced by the dopamine agonist apomorphine in rats. Injection of 0.032 mg/kg apomorphine i.v. caused 86 % reduction in neuronal firing in vehicle-treated animals, which was shifted to 56 % suppression in animals pre-treated with iloperidone (1 mg/kg i.p.). After pre-treatment with either haloperidol (0.25 mg/kg i.p.) or clozapine (20 mg/kg), apomorphine suppressed neuronal transmission by 7 % and 50 %, respectively. Hence, iloperidone and clozapine affected apomorphine-induced reduction of dopaminergic activity in the SNC to a lesser extent than observed for haloperidol.

Typical and atypical antipsychotic agents differ in their interactions with presynaptic dopamine autoreceptors in the striatum. To further elucidate the binding properties of iloperidone, its antagonistic effect on these autoreceptors was tested. The induction of L-DOPA by Gamma-butyrolactone (GBL) in rats was down-regulated by apomorphine. Iloperidone doses of 0.3, 1, 3 and 10 mg/kg i.p. reversed the inhibition of L-DOPA accumulation by apomorphine by 0, 29, 33, 42 and 40 %, respectively. Likewise, the iloperidone metabolites P88 (10 and 30 mg/kg i.p.) and P89 (0.3 and 3.1 mg/kg i.p.) reversed the antagonistic effects of apomorphine on GBL treatment. Clozapine also partially reversed the block of L-DOPA accretion by 17, 0, 63 and 2 % at 10, 30, 60 and 100 mg/kg each. On the contrary, administration of 0.03, 0.1, 0.3 and 1 mg/kg haloperidol potently loosened the inhibition of L-DOPA increase by 12, 34, 71 and 100 %. Consistent with the binding profile of an atypical antipsychotic, iloperidone, P88, P89 and clozapine revealed slight to moderate dopamine autoreceptor antagonism.

2.3.7. Antagonistic effects of iloperidone on serotonergic and adrenergic receptors in vivo

Antagonism at 5-HT_2 receptors concomitant to the inhibition of dopamine D_2-receptors has been suggested to account for the reduced EPS potential of atypical compared to typical antipsychotic agents. Chronic treatment of rats with 5 mg/kg/day i.p. iloperidone did not significantly change the number or affinity of D_2-receptors in the striatum or nucleus accumbens. The same treatment significantly down-regulated cortical 5-HT_2-receptors in the frontal cortex to 41-59 % of the control level, which is in agreement with effects produced by clozapine. In contrast, haloperidol did not affect 5-HT_2-receptors. Hence, iloperidone showed the characteristic activity of an atypical antipsychotic in this test.

However, 3 or 10 mg/kg s.c. iloperidone failed to interfere with 5-HT_{1A} agonistic activity of 0.1 mg/kg s.c. 8-OH-DPAT. This suggests that iloperidone does not exert 5-HT_{1A} antagonism *in vivo*, which contrasts earlier *in vitro* findings (see section 2.3.3.).

The capability of iloperidone to antagonise other serotonergic and also α1-adrenergic receptors was investigated in pithed rats. Iloperidone at 1 and 6 mg/kg p.o. doses inhibited the diastolic blood pressure increase produced by i.v. administration of the α1-adrenergic receptor agonist phenylephrine by 6- and 32-fold, respectively, and also non-competitively blocked the effect of serotonin. This indicates the potential of iloperidone to evoke hypotension in response to antagonism at vascular α1-adrenergic and 5-HT_2-serotonergic receptors.

Moreover, iloperidone protected against norepinephrine-induced lethality in rats (ED_{50} = 0.3 mg/kg i.p.), indicating effective blockade of peripheral α-adrenergic receptors by iloperidone.

2.3.8. Effects of iloperidone and its metabolites on dopamine-, serotonin- and adrenalin-mediated behaviours

The antagonistic mode of action of iloperidone at dopamine, serotonin and adrenalin receptors *in vivo* was additionally confirmed in several behavioural animal models.

Overall, the results of behavioural assays conducted in mice, rats, and monkeys indicate potential efficacy of iloperidone for the treatment of both positive and negative symptoms of schizophrenia, including potential anxiolytic activity in the absence of sedative effects. Results also indicate decreased potential for EPS liability in comparison to typical antipsychotics such as haloperidol.

The primary pharmacodynamic properties of iloperidone and its main metabolites P88, P89 and P95 have been analysed in numerous in vitro, ex vivo and in vivo studies, mostly in comparison to clozapine and haloperidol. These investigations confirm the antagonistic profile of iloperidone at dopaminergic, serotonergic and adrenergic receptors, which is characteristic for the class of atypical antipsychotic agents.

Secondary pharmacodynamic studies

Iloperidone showed dose-dependent analgesic activity in a pain model testing writhing behaviour in Swiss CD-1 mice induced by phenylquinone (ED_{50} = 0.03 mg/kg s.c.).

Compared to clozapine, iloperidone did not antagonise lethality induced by the acetylcholine esterase inhibitor physostigmine from 30 to 120 min post administration of a 40 mg/kg i.p. dose. This additionally confirms absence of anticholinergic properties of iloperidone.

Results from these investigations add to the pharmacological profile of iloperidone, but are insignificant in terms of the proposed indication

Safety pharmacology programme

2.3.9. Cardiovascular system

2.3.9.1. *Effects of iloperidone and its P88 and P95 metabolites on the hERG current and action potential parameters*

In view of the potential of many antipsychotic drugs to elicit prolongations of the QT interval, iloperidone and its metabolites P88 and P95 were evaluated for hERG interaction and effects on cardiac action potential and depolarisation parameters in dog Purkinje fibres *in vitro*.

In a comparative analysis of iloperidone, P88, P95, risperidone and ziprasidone on mammalian cells that stably expressed the HERG channel, all test items revealed rapid and reversible blockade of hERG currents (Table 3). In terms of IC_{50}, the order of potency was iloperidone > ziprasidone ≈ P88 > risperidone > P95. At a temperature of 34-35°C, i.e. close to the physiological level, IC_{50} concentrations increased except for risperidone. In particular, the IC_{50} value of P95 was almost 3-fold elevated. This indicates that any contribution of P95 to the QT prolongations elicited by iloperidone is presumably without relevance.

In addition, the effects of iloperidone, P88 and P95 on ventricular Purkinje fibres prepared from male dogs were investigated at concentrations of 0.01, 0.1, 1 and 10 µM. At the end of the experiment,

vehicle (= DMSO)-treated fibres were exposed to the inhibitor of I_{kr} potassium channels and β-adrenergic receptors dl-sotalol hydrochloride to confirm sensitivity of the preparations.

Table 1: Inhibition of hERG currents by iloperidone and its metabolites in comparison to risperidone and ziprasidone.

Test article	hERG IC_{50} [nM]	hERG IC_{50} at 34-35°C [nM]
Iloperidone	29	37
P95 metabolite	4,319	12,789
P88 metabolite	56	100
Risperidone	394	188
Ziprasidone	55	79

At stimulation frequencies of 0.5 and 1 Hz, both iloperidone and P88 concentration-dependently prolonged action potential duration (APD; Figure 1). Effects were already apparent at the lowest iloperidone dose of 0.01 µM. At 1 Hz, statistically significant effects were apparent for iloperidone and P88 at 1 µM for APD_{60} and at ≥ 0.1 µM for APD_{90}, respectively. At 0.5 Hz, statistically significant influences on APD_{60} and APD_{90} were obvious for iloperidone and P88 at ≥ 1 µM. At 10 µM iloperidone and P88, the plateau phase appeared depressed taking a triangular shape. Moreover, the maximum rate of depolarisation was reduced at 10 µM iloperidone or P88 and 3 Hz.

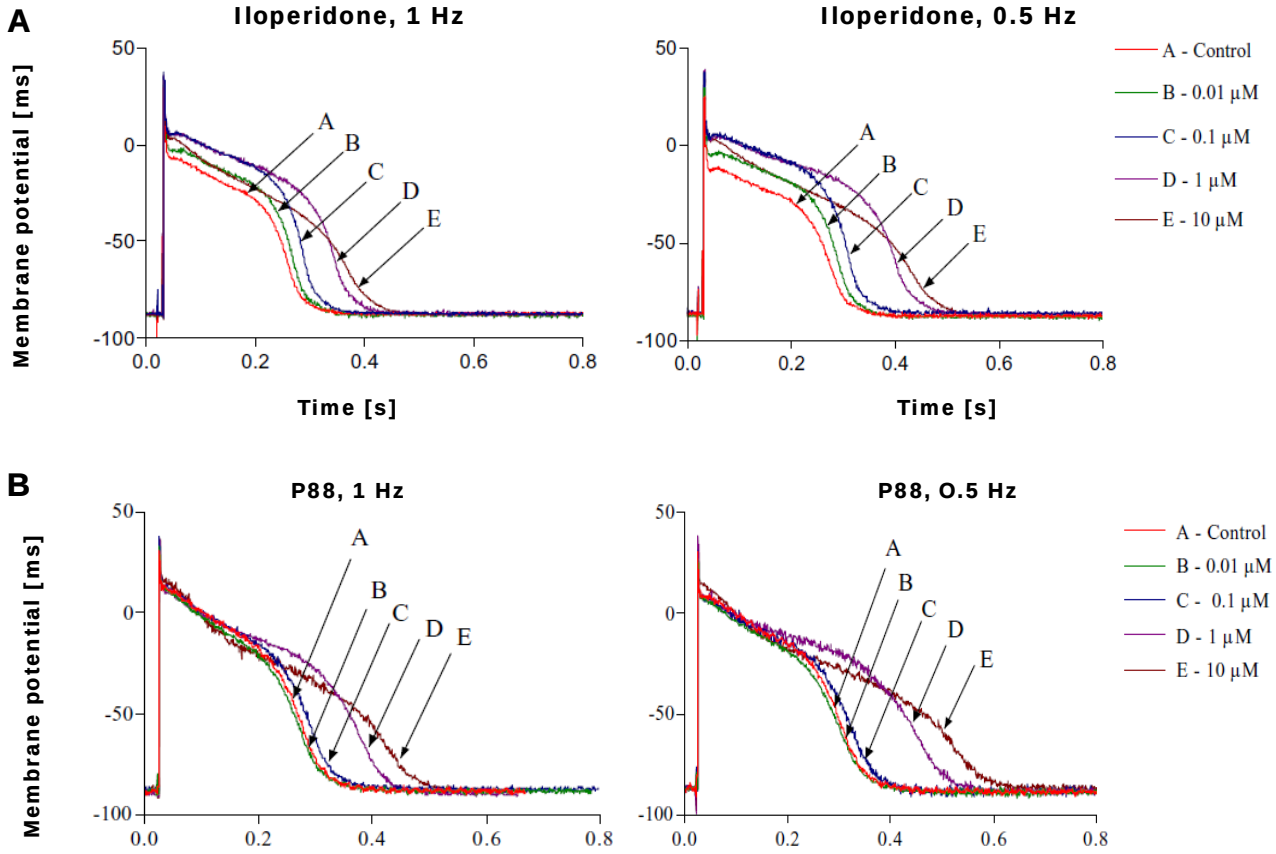


Figure 1: Effects of iloperidone and P88 on action potentials in dog Purkinje fibres.

Time [s] **Time [s]**

The concentration-dependent prolongation of APD is shown at stimulation frequencies of 1 and 0.5 Hz for iloperidone (A) and its metabolite P88 (B).

Thus, iloperidone reveals effects on APD that are characteristic for a pure K^+ channel blocking agent. In contrast, no significant effects on action potential duration or maximum rate of depolarisation were determined with P95, albeit prolongations of action potential durations were noted at 10 µM. Compared to iloperidone, P88 and P95, sotalol prolonged APD at substantially higher concentrations of 50 µM.

2.3.9.2. *Effects of iloperidone and its P89 metabolite on haemodynamic parameters*

In receptor interaction studies and subsequent pharmacodynamic investigations *in vivo*, iloperidone antagonised α1-adrenergic receptors, leading to hypotensive effects. For this reason, the influence of iloperidone on haemodynamic parameters such as blood pressure, heart rate, cardiac output and ECG was assessed.

Initially, 10 mg/kg iloperidone was orally administered to conscious normotensive Long Evans rats (n = 4). No effect on arterial pressure or heart rate was apparent, although one rat showed a 41 % decrease in mean arterial pressure at 90 min. Furthermore, a statistically significant reduction was observed among all animals at 240 min, which was rated biologically irrelevant. In a second study in these rats, 3 mg/kg p.o. doses of iloperidone (n = 3) elicited a maximal decrease of 13 % in mean arterial pressure, whereas heart rate was diminished by 5 %. In contrast, 10 mg/kg p.o. clozapine (n = 4) increased mean arterial pressure and heart rate.

In conscious spontaneously hypertensive rats, oral iloperidone doses of 1 and 3 mg/kg (n = 4/group) decreased arterial pressure by 11 % (1 mg/kg) and 13 % (3 mg/kg), respectively. Likewise, heart rate was reduced by 16 bpm at 1 mg/kg and 10 bpm at 3 mg/kg.

When a lower oral dose of 0.3 mg/kg was compared to 1 mg/kg iloperidone, no effect on blood pressure or heart rate could be confirmed in this rat model. However, a 48 % inhibition of the hypertensive response to the α_1-adrenergic receptor agonist phenylephrine was determined with 1 mg/kg iloperidone. At higher dosages of 6 (n = 4) and 20 mg/kg p.o. iloperidone (n = 6), blood pressure was reduced by 45 %, while phenylephrine inhibition increased to 89 %. Again, 10 mg/kg clozapine (n = 4) increased mean arterial pressure and heart rate by 18 bpm.

Consistent with these findings, iloperidone (0.02 - 1 mg/kg i.v.) dose-dependently lowered arterial pressure in anaesthetised dogs (39 %). However, no effects on heart rate, cardiac output and ECG were noted. The induced hypotension was rapid in onset with bolus injection (within 5 min) and gradually increased upon slow infusion (over 30 min). Plasma levels after i.v. bolus injection of 0.02 mg/kg iloperidone, ranged from 5 – 96 ng/ml with an average C_{max} of 63 ng/ml ± 24 ng/ml (n = 4), while after slow infusion concentrations were 5 – 24 ng/ml with an average C_{max} of 15 ng/ml ± 8 ng/ml was determined (n = 3).

In conscious dogs, orally administered iloperidone (2 and 5 mg/kg) decreased mean arterial pressure by 22-24 %, respectively (n = 3 and 4, respectively). A telemetry study in dogs with repetitive oral dosing of 0, 5 and 15 mg/kg iloperidone on days 1, 4 and 7 confirmed the reduction in blood pressure at mid and high dose levels (n = 2/sex/group) and a transient increase in heart rate at the high dose level, but did not reveal perturbations of ECG or body temperature.

Hypotension and reduced peripheral vasodilatation was also obvious following intraduodenal administration of iloperidone (0.5, 1, 2 and 10 mg/kg) to anaesthetised dogs. Again, no ECG changes were apparent.

Intraduodenal administration of 2 mg/kg of the metabolite P89 similarly diminished mean arterial blood pressure by 17 %, decreased heart rate by 14 % and concomitantly increased peripheral resistance (+16 %). Effects were more prominent after i.v. injection of 2 mg/kg P89 (arterial blood pressure -34 %; heart rate -25 %, peripheral resistance -35 %). As seen for the parent compound, no ECG alterations were eminent.

Overall, these studies indicate a dose-dependent hypotensive effect of iloperidone and its P89 metabolite via blockade of α_1-adrenergic receptors. The differences seen between iloperidone and clozapine might be explained by different antagonism at α_1-adrenergic receptors.

2.3.10. Respiratory system

Single oral doses of iloperidone (0.1, 1 and 10 mg/kg) or its metabolite P95 (1, 10 and 100 mg/kg) did not adversely affect respiratory parameters (respiratory rate, tidal and minute volume) in a plethysmography study in SD rats. Minor decreases in minute volume were observed upon iloperidone administration ≥ 1 mg/kg and all P95 doses, but remained within limits of healthy untreated controls and were hence regarded irrelevant.

2.3.11. Central nervous system

Single gavage doses of 10, 30, 100 or 300 mg/kg P95 produced neurobehavioural effects at all dose levels in male CD-1 mice. Ataxia, hyposensitivity to sound, slightly to severely decreased motor activity, ptosis, and/or impaired righting reflex were observed in animals at doses of ≥ 30 mg/kg. These effects were less pronounced at 10 mg/kg. Neurobehavioral signs were resolved in most animals at doses of ≤30 mg/kg at the 6 h observation time point, while the signs dissipated at doses of ≥100 mg/kg after 24 h.

Among clinical signs, significant decreases in body temperature were obvious at all dose levels. Moreover, relaxed scrotums were noted in several animals at doses ≥ 30 mg/kg on study day 1, which dispelled on the second day.

2.3.12. Inhibition of cytochrome P450 enzymes by iloperidone and its P88 and P95 metabolites in vitro

In human liver microsomes, iloperidone inhibited CYP2D6 and CYP3A4/5 with an IC_{50} of 2 µM and K_i values of 1.36 and 2.53, respectively, but did not block CYP1A2, 2C8, 2C9, 2C19 and 2E1. Among the tested CYP enzymes, P88 only weakly inhibited CYP2D6, whereas no blockade was determined for P95.

As a loss of enzymatic activity had been observed in this study independent of the incubation with one of the test articles, the inhibitory potential was assessed in another experiment. This second study revealed 22, 48, 45, 60, 86, 96 and 92 % inhibition of CYP1A2, 2C8, 2C9, 2C19, 2D6, 3A4 and 3A5, respectively at 100 µM iloperidone. IC_{50} values were > 100 µM for CYP1A2, 2C8 and 2C9, whereas 57, 11, 8.5 and 2.1 µM were each determined for CYP2C19, 2D6, 3A5 and 3A4. A time-dependent effect was detected for CYP2D6 and 3A4/5 after iloperidone pre-incubation.

At 100 µM concentration, the P88 metabolite directly inhibited CYP2C9, CYP2C19, CYP2D6, and CYP3A4/5, with approximately 25%, 24%, 76%, 43% and 30% inhibition, respectively. IC_{50} values were > 100 µM for CYP2C9, 2C19 and 3A4/5 or 35 µM in case of CYP2D6. Evidence of time-dependent inhibition of CYP2D6 and CYP3A4/5 by P88 was also observed.

In contrast, P95 showed little or no potential to directly inhibit the aforementioned cytochrome isoforms and the IC_{50} values for these enzymes were all above 100 µM. In addition, there was little or no evidence of time-dependent inhibition.

Based on the aforementioned IC_{50} values and the steady-state C_{max} of 19.33 ng/ml or 45 nM determined at the proposed maximally daily dose of iloperidone in human subjects (12 mg b.i.d.), iloperidone displays an inhibitory potential for CYP2D6 and 3A4/5 isozymes. Nevertheless, an inhibition of CYP2C19 or CYP1A2, 2C8 and 2C9 isoforms by iloperidone can be considered highly unlikely in view of large safety margins of > 1000-fold with regard to clinically relevant exposure.

2.3.13. Induction of cytochrome P450 enzymes by iloperidone and its P88 and P95 metabolites in vitro

The ability of iloperidone and the P88 and P95 metabolites to affect expression of CYP enzymes was analysed in primary human hepatocytes. Cultures were treated once daily for three consecutive days with 0.05, 1 or 20 µM iloperidone, P88 or P95, or one of the CYP inducers omeprazole and rifampin. In microsomes prepared from these cultures, CYP activity was determined by means of phenacetin O-dealkylation (CYP1A2), amodiaquine N-dealkylation (CYP2C8), diclofenac 4'-hydroxylation (CYP2C9), S-mephenytoin 4'-hydroxylation (CYP2C19) and testosterone 6β-hydroxylation (CYP3A4/5).

Iloperidone or P88 increased CYP1A2 and 2C8 activity to a minor extent (2-fold or less). However, 20 µM iloperidone or P88 showed potential to interfere with CYP2C9, 2C19 and 3A4/5 activity, which reached statistical significance only for CYP3A4/5. The decrease in activity was approximately 30, 47, and 79 % for iloperidone and about 19, 45 and 80 % for P88. In contrast, treatment of hepatocytes with P95 had little or no effect on any of the CYP enzymes examined.

Iloperidone, P88 and P95 did not exert a significant potential to induce cytochrome P450 enzymes. However, iloperidone and P88 showed significant inhibitory potential for CYP2D6 and 3A4/5.

2.3.14. Pharmacokinetics

Iloperidone and its metabolites P88 and P95 are rapidly absorbed across species with oral absorption rates of 50 % to 80 % in the mouse, 56 % to 86 % in the rat, 76 % to 79 % in the rabbit, and 42 % to 99 % in the dog. However, low bioavailability was observed in all species with apparent differences. This is attributed to an extensive first-pass metabolism. The oral bioavailability was 5 % in the mouse, < 1% in the rat, and 19 % in both the rabbit and the dog.

Apart from mice, higher exposures of female animals were particularly evident in rats, while a trend towards elevated exposures was also obvious in dogs. These gender differences are consistent with clinical observations (see clinical AR).

Iloperidone and P95 are extensively bound to plasma proteins in the various test species including humans. Both compounds are quickly distributed into various tissues reaching highest concentrations in liver, gastrointestinal system and bladder. Iloperidone showed also affinity to pigmented tissue and was retained for a prolonged time in the pigmented eye. This accumulation of iloperidone in skin and uveal tract indicates melanin-binding activity.

Iloperidone and P88 revealed potential to permeate the blood-brain-barrier. Whilst P95 was not detected in the brain in the performed autoradiography study it still exerted CNS-related effects suggesting some level of blood-brain permeation anyhow. It should be noted that iloperidone was not detected in the brain in a similar autoradiography study but only in a study specifically designed to quantitate levels in brain tissue.

Despite potential to cross the placenta, the iloperidone concentrations in maternal liver were 10- to 20-fold greater than in foetal liver. However, iloperidone is extensively transferred into milk reaching 10-times higher levels compared to plasma.

Iloperidone is extensively metabolised in mice, rats, rabbits and dogs. While the metabolites P22, P94 and P88 are principally found in humans, predominant metabolites in animals are P89 in mice, open-ring iloperidone in rats as well as P20.8, P28, P88, P89, P94 and P95 in rabbits and dogs.

The metabolic profile of the dog suggests that the dog could be a relevant non-rodent species for toxicological evaluation of iloperidone, except for the low levels detected of the metabolite P88.

The metabolic profiles of rodent species indicate that the major human metabolite P95 is not formed in sufficient amounts to allow a complete toxicological evaluation. Following oral iloperidone administration to rabbits, P88 and P95 were detected in plasma at levels reaching 2/3 and 1/3 of iloperidone levels, suggesting that the rabbit is a relevant species for reproductive toxicity.

No preclinical pharmacokinetic drug interaction studies other than *in vitro* CYP inhibition/induction studies were performed. Interaction was studied in the clinical setting. This is acceptable from a preclinical viewpoint.

Iloperidone, P95 and P88 are mainly eliminated by faeces in all animal species examined, whereas urine is the main excretion route in humans. In the mouse and the rabbit, significant amounts were also found to be excreted via urine.

2.3.15. Toxicology

Single dose toxicity

Six GLP-compliant single/acute-dose toxicity studies with iloperidone were conducted in rats and mice following oral, intravenous and intraperitoneal routes of administration. Approximate median lethal oral doses following single administration to mice were found to be in the range of 55 and 80 mg/kg (males) and <55 (females) mg/kg. In rats the median lethal doses were significantly higher with >480 mg/kg in males and between 240 and 480 mg/kg in and females, respectively.

Repeat dose toxicity

Repeat-dose toxicology studies with iloperidone were conducted in mice, rats, rabbits and dogs up to 3 months in mice, 6 months in rats and 12 months in dogs following oral, intravenous or inhalative routes of exposure. In compliance with the clinical administration, oral administration (gavage) was the primary route in nonclinical studies. CNS related toxicity elicited iloperidone was consistently noted across species.

In mice, oral administration of iloperidone at 5, 10 and 20 mg/kg/d for 13-weeks caused early deaths and lymphoid necrosis of multiple lymphoid organs. Histological findings in lymphoid organs were interpreted to be induced secondary by elevated systemic levels of glucocorticoids released by the adrenal cortex in response to stress. Due to the severe toxicity/high death rate observed in this study, the clinical relevance of these findings seems to be questionable. No similar findings in lymphoid organs were reported from other test species or clinical studies in humans. MTD was determined to be 5 mg/kg.

Repeat-dose toxicology studies with iloperidone in rats resembles those of already approved comparable drugs and mainly consisted of findings related to the CNS (ptosis, relaxed scrotums) and prolactin stimulation due to exaggerated pharmacodynamic activity of iloperidone, i.e. antagonistic activity at D_2-, 5-HT_{2A}- and α1-adrenergic receptors. As expected PRL release was enhanced in rats. However, prolactin levels were only measured in the carcinogenicity study in rats. Hyperprolactinaemia was associated with changes in mammary gland (vacuolization, hyperplasia), female genital tract (uterus weight), with additional effects on the male accessory sex organs (testes and prostate) at

higher exposures. Changes in body weight, body weight gain and food consumption were also noted. It should be stated that increased PRL levels were also observed in patients, but corresponding side effects were rare and are appropriately reflected in the proposed SmPC. Among other findings in toxicity studies, effects on mean haematology- and serum chemistry values were observed. Although statistically significant, the findings were generally within normal limits of variation; hence toxicological relevance was considered to be unknown and of low clinical relevance.

Repeat-dose toxicology studies conducted in Beagle dogs were primarily related to CNS events including decreased spontaneous activity and/or crouching posture, tremors, bizarre behaviours, laboured breathing, scleral infection, ptosis of the eyelids, prolapsed nictitating membranes, and glassy eyes.

In the 12-months chronic toxicity study in dogs, there was a pronounced variability in exposure between dogs. The Applicant claimed that rate of absorption in the dog is rapid after a single dose with a t_{max} range of 0.5-1 h, but slow, up to several hours, after multiple dosing. However, these differences in t_{max} after single or repeat-dose administration, make it even more notably that none of the 8 dogs receiving the highest dose (24 mg/kg) had detectable levels above the limit of quantification (LOQ of 2 ng/ml) after 4 h on Day 1 after they had received a single dose only. Moreover, at the last measuring point in Week 49, two out of four male dogs of the high dose group had plasma levels below LOQ, while levels of the other two males were determined as 3.40 ng/ml and 115.26 ng/ml, respectively. A similar pattern of exposure, or lack of exposure, was seen for both sexes in other dose groups at both sampling points. Nevertheless, in the study report and in the written summaries, averages based on the inadequate kinetic data were calculated and presented for risk assessment. For example, the average presented by the Applicant for males of the high dose group in Week 49 of the study is 118.66/4 = 29.7 ng/ml, which is a mathematically correct mean, but in this context has to be considered misleading as it implies that all dogs had measurable levels of iloperidone.

Taken together, the kinetic data from the 52-week study cannot be used as an argument that the chronic toxicity of iloperidone has been evaluated in the dog, nor can it be used for comparisons with maximum human exposure or for risk assessment. In the 4-week toxicokinetic study (0494-220), using the same administration and formulation as in the 52-week study, an AUC of approximately 700 ng/ml*hr was reached at 25 mg/kg, which is just barely above maximum human exposure.

It should be further noted that serum prolactin levels were not determined in Beagle dogs. Hence, it is unknown whether iloperidone has affected serum prolactin levels in dogs. However, prolactin related findings were not reported in the 13-week and the 12-month oral toxicity studies performed with iloperidone in dogs.

P95 is the primary metabolite of iloperidone in humans with approximately 6 – 9 fold higher amounts when compared to rats and mice. In contrast to the rodent species, the proportion of the P95 metabolite in dogs and rabbits is better comparable to those in humans. Due to this proportional difference in exposure to P95 following iloperidone administration in preclinical species compared with that in human, twelve toxicology studies in rats and mice were conducted with the pure P95 metabolite. The extensive toxicological programme conducted with P95 included an acute toxicity study in mice, two 13-week and a 26-week oral repeat-dose toxicity studies in rats, a full battery of *in vitro* and *in vivo* genetic toxicity tests, an embryo-foetal development- and a two year carcinogenicity study in rats. Furthermore, immunotoxicity was evaluated in conjunction with iloperidone in rats and the phototoxic potential of the P95 and P88 metabolites was assessed in a neutral red uptake tests using Balb/c 3T3 fibroblast cells.

In sum, the chronic administration of P95 to rats produced microscopic alterations in the adrenal, pituitary, thyroid, mammary gland, ovary, and female reproductive tract. Effects on oestrous cycle, thyroid, and mammary gland alterations persisted following a 4-week recovery period. An increase in

BrdU labelling indices which indicates cellular proliferation was found for mammary gland, pituitary, and endocrine pancreas. The clinical signs and tissue changes are widely compatible with the pharmacological effects of activity at the dopamine and/or adrenergic receptors, alike the parent compound iloperidone. However, since no BrdU analysis was performed in the iloperidone 26-week study, no comparisons to the parent compound are possible. In order to further evaluate the observed proliferation in various tissues, a 2-year carcinogenicity study in rats was subsequently performed.

Of note, P95 was found at low levels in 22 out of 60 controls samples, and further, P95 and P95 conjugates were also found in the urine sampled at Week 26, suggesting misdosing, rather than mixing up of samples during analysis. The levels of P95 in plasma and P95 and conjugates thereof in urine, were low compared to dosed samples. Even if a contamination of one third of the controls is remarkable, since no unexpected effects were seen, it is not considered to seriously impact the conclusions drawn.

Regarding the other human metabolite, P88, an interconversion between iloperidone and P88 was demonstrated in a GLP study in rats at single oral gavage doses of 2, 10 or 50 mg/kg P88. This interconversion resulted in a higher exposure of iloperidone compared to P88 and was more prominent in females than in males. P88 is formed from iloperidone by reduction of the carbonyl of the acyl side chain. Thus, assessments of exposure in the rat can be made on a sum of the two compounds. Since only one species is necessary for the evaluation of metabolites, P88 is regarded as sufficiently evaluated in the nonclinical programme through studies in rats administered iloperidone (chronic toxicity study, micronucleus assay, carcinogenicity study) and also by the whole reproductive toxicity programme, since rabbit also produces P88 to a great extent.

Further, P88 was devoid of any genotoxic potential up to the limit of toxicity in an Ames test and a chromosomal aberration assay. Hence, P88 is regarded to hold no genotoxic potential.

Genotoxicity

Iloperidone and its major human metabolite P95 were tested for genotoxicity in standard batteries meeting ICH guidelines with no evidence for clinically relevant genotoxic potential.

Carcinogenicity

Three carcinogenicity studies were conducted. Iloperidone was tested in 2 year bioassays in mice and rats and P95 was tested in a 2 year study in rats.

In the mouse bioassay with iloperidone, an increase in mammary adenocarcinoma was observed with unclear relevance as it was significant only in the low dose. The incidences of mammary duct ectasia/galactoceles, glandular hyperplasia, and uterine adenomyosis were increased in all female dose groups. These findings are well known effects in rodents administered antipsychotics which cause increased prolactin levels secondary to the inhibition of the dopamine receptor. Prolactin levels were monitored during the study and were increased 4 to 9 times compared to controls in both males and females. Non-neoplastic histopathological changes consisted of cardiomyopathy and/or atrial thrombosis and chronic interstitial inflammation/fibrosis and alveolar macrophages in both males and females. Cardiomyopathy is a common finding in aging mice, however, the increase in severity and incidence in all treated groups suggests that iloperidone worsen this effect. Moreover, the increased incidence of atrial thrombosis, 7/0, 3/1, 9/4, 12/10, 12/15 in males and females in two control groups and in 2.5, 5 and 10 mg/kg dose groups, respectively, is also considered to be treatment related and occurred at a level similar to the maximum human exposure. The mechanism underlying the increased incidence of cardiomyopathy and atrial thrombosis in mice is unknown. Clinically, there have been no reports of cardiomyopathy and atrial thrombosis.

The findings in the lung, chronic interstitial inflammation/fibrosis and alveolar macrophages, are considered secondary to the cardiac changes. The survival rate of females in this carcinogenicity study was only to 35 % in the high dose group at Week 82, when this group was terminated. This reduced the power of the study to fully evaluate the carcinogenic potential in female mice. In the highest dose group, 10 mg/kg, the exposure margin to human maximum exposure was approximately 3.

No relevant increase in tumour incidence was observed in the rat study. However, the relevance of carcinogenicity studies with iloperidone is questionable as exposure levels were around the human therapeutic exposure or lower.

In the 2 year study in rat with P95, significant increases in adenoma in pancreatic B- islet cell and pituitary *pars distalis* occurred already at the lowest dose. This is considered to be a consequence of prolonged hyperprolactinaemia and prolonged loss of dopamine signalling, respectively, and was expected after treatment with an atypical antipsychotic drug. Increased prolactin levels were seen in both female and male rats throughout the study. In the kidney, chronic progressive nephropathy was seen at all doses in females and in males, and tubular adenoma was seen in two females given 400/250 mg/kg/day. The incidence of 3.6 % was not statistically significant and fell outside the historical control data. The Applicant suggests that the presence of renal cortical tubular adenoma in females was due to persistent renal activity in the excretion of the test material, which seems acceptable. Clinically there have been no reports on renal adverse events. The exposure of P95 to these females compared to maximum human exposure of P95, based on AUC, is approximately 40-times higher. It is unlikely that the renal toxicity seen in the carcinogenicity study of P95 in rats is relevant to human safety assessment.

Reproduction Toxicity

All studies submitted for the assessment of reproductive toxicity of iloperidone had been performed prior to the introduction of ICH S5, which is reflected in the study design used in two studies. While one study corresponds in most aspects to a combination of a fertility, a prenatal development, and a pre- and postnatal development study (in the following called Segment I/II/III study), the other one constitutes rather a peri- and postnatal study than a pre- and postnatal study as treatment had not been started until gestation day 17.

Separate prenatal developmental studies had been conducted in rats and rabbits. Furthermore a prenatal development study with the major metabolite P95 had been performed in 2000 in rats. No data is available on plasma levels in these studies (except for the P95 SEG II study). Instead the Applicant has related and discussed the doses to plasma doses in non-pregnant animals. The exposure estimations are therefore of limited value, toxicokinetics evaluations were not performed, and so exposures were estimated in the rat from a 4-week toxicokinetics study. For the rabbit, the exposures from a single dose were used; however, as only single dose data for the non-pregnant rabbit are available, only the mg/m^2 values are used as comparators.

In adult animals iloperidone induced a dose-dependent increase in clinical signs which can be related to the pharmacodynamic action of the substance. Iloperidone had no effects on male fertility in rats up to a dose of 36 mg/kg/d ($NOAEL_{fertility}$ 36 mg/kg/d, rat/human exposure margin based on AUC: 17.2).

In female rats treated with iloperidone fertility was impaired by cycling disturbances, a decreased number of corpora lutea and, as a consequence, a reduced number of implantation sites at doses greater than 4 mg/kg/d (NOAELfertility: 4 mg/kg/d → rat/human exposure margin based on AUC: 0.5). These effects might be related to an increase of prolactin levels as demonstrated in the carcinogenicity studies performed in rats and mice.

The duration of pregnancy was significantly prolonged when pregnant rats were treated with iloperidone either during the whole gestation period (Segment I/II/III study) or during late gestation (Perinatal and postnatal development study), respectively.

In rats, prenatal and postnatal growth and survival of the F1-generation was significantly decreased at iloperidone doses that also induced maternal toxicity (NOAEL: 4 mg/kg/d → rat/human exposure margin based on AUC: 0.5). No teratogenic potential was observed, however, a significantly increased incidence of skeletal variations (significantly increased number of fetuses and litters with dislocated, fragmented or dysplastic thoracal vertebra centra and significantly decreased number of fetuses with ossification of hindpaw phalanges III in the high dose group; significantly decreased number of fetuses with ossification of caudal vertebral centra and metacarpus and significantly increased number of fetuses with anlage of 14th thoracic vertebra and analogous 14th rib in the mid and high dose group, respectively) was observed in the prenatal development study and visceral variations (dilatation of lateral and third brain ventricles, dilatation of ventricle(s) of the heart in the high dose group) in the Segment I/II/III study in rats, respectively. In rats, the development of landmarks was not significantly affected by treatment of the dams with iloperidone during gestation and lactation. In the open field test the overall pattern of activity was similar in all groups with a decrease in activity noted over the 20-minute time periods on postnatal day 22 and 60, however, on postnatal day 22 significantly higher mean activity counts were noted for single 20-minute blocks in mid dose pups. A similar pattern was also observed in high dose offspring, but the sample size was too small to draw any conclusion. Learning, memory, and re-learning were unaffected and no effects were seen on F1 fertility, pregnancy, and F2 development until the day of birth.

In a prenatal development study in rabbits, effects on embryo-foetal development were only observed at maternotoxic iloperidone doses (NOAEL: 10 mg/kg/d → no toxicokinetic data available). In the high dose group a significantly increased incidence of foetuses with organs not occurring in the proper position and/or orientation (transverse or displaced) was noted (stomach: transverse position or displaced dexter, enlarged or enlarged and taut with soft mass or fluid) affecting 25% of the foetuses of this dose group (7 fetuses/7 litters) as well as a dose-dependent, but not statistically significant increase of foetuses with left kidneys in transverse position or displaced in caudal or cranial region. In each group a single malformed foetus was observed, however, the malformations were varying and without any pattern.

Other toxicity studies

Phototoxic potential

Iloperidone showed a possible phototoxic potential in the *in vitro* neutral red uptake test in Balb/c 3T3 fibroblasts. Moreover, tissue distribution studies with orally treated pigmented rats and rabbits revealed iloperidone binding to melanin-containing structures and high tissue radioactivity concentrations were measured in the uveal tract. Despite these findings, a clinically meaningful phototoxic *in vivo* potential can most probably be excluded, since ocular toxicity was neither evident in preclinical studies of non-rodent species, nor during ophthalmological examinations performed in clinical trials.

Impurities

The specification limits for impurities Q2, Q4, and Q7 have been qualified through nonclinical toxicology studies according to the ICH Q3A (R2) guideline. The specifications for the Q2 and Q4 impurities have been tightened from the previously proposed limits of NMT 0.50 % and NMT 0.20 %, respectively, to a revised proposed specification of NMT 0.15 %, which is at the qualification threshold. In compliance with the guideline on the Limits of Genotoxic Impurities, the sum of the three potentially genotoxic impurities (Y8B, Y8A, and 1-bromo-3-chloropropane) is not more than the TTC of 1.5 µg/day

or, based on a 24 mg maximum daily dose, NMT 62.5 ppm/day. With a proposed specification of NMT 5 ppm for each of the three potentially genotoxic impurities, the sum of these impurities will be NMT 15 ppm, which is well below the TTC.

2.3.16. Ecotoxicity / environmental risk assessment

Table 1. Summary of main study results

Substance (Iloperidone Tablets): Iloperidone			
CAS-number (if available):133454-47-4			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD107	Study report not available	
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC $_{surfacewater}$	0.12	µg/L	> 0.01 threshold (Y);
Phase II Physical-chemical properties and fate			
Study type	**Test protocol**	**Results**	**Remarks**
Adsorption-Desorption	OECD 121	K_{oc} =1,000,000	Indicative test only

No conclusion on the environmental risk of Iloperidone can be made as the applicant failed to submit some studies requested for this purpose. A phase II tier of ERA is required based on the submitted data. Furthermore no final conclusion on the PBT properties of iloperidone can be drawn as the applicant failed to confirm the Kow submitted with the official study report.

The applicant should have provided a complete environmental risk assessment according to the guideline (EMEA/CHMP/SWP/4447/00, June 2006) and the Question and Answer Document (EMA/CHMP/SWP/44609/2010, March 2011). All recommended tests should be conducted. No tests can be waived. The ERA should be provided including all study reports for evaluating the test quality.

2.3.17. Discussion on non-clinical aspects

Iloperidone shows the receptor binding profile well known from other members of the class of atypical antipsychotic drugs. Most characteristically for this class of agents is the higher affinity to 5-HT_{2A} compared to D_2 receptors suggesting a reduced propensity for EPS development in comparison to typical antipsychotics like haloperidol. These activities of iloperidone were confirmed in a variety of animal models of serotonin- and dopamine- mediated behaviours demonstrating the affinity of iloperidone for mesolimbic dopaminergic neurons and hence point towards effective treatment of schizophrenia, including potential anxiolytic activity in the absence of sedative effects.

The torsadogenic potential of iloperidone seems to be higher when compared to most other antipsychotic drugs. Prominent blockade of hERG currents was determined with IC50 values of 29 nM for Iloperidone and 56 nM for the P88 metabolite, hence demonstrating higher affinity to hERG channels when compared to most other antipsychotic drugs. In agreement with these findings, iloperidone and P88 concentration-dependently prolonged action potential duration in dog ventricular Purkinje fibres at concentrations of 10 nM and above. Only at a high concentration of 10 µM of iloperidone and its P88 metabolite, some reduction of the maximum rate of depolarization was observed (indicating slight cardiac Na+ current block), and a slight reduction of APD60 was observed (indicating slight cardiac Ca2+ current block). Therefore, iloperidone and its P88 metabolite reveal effects on the action potential duration of dog ventricular Purkinje fibres that are characteristic for a pure K+ channel blocking agent.

Despite these findings, no effects on the ECG were observed in several studies in dogs after doses of ≤ 1 mg/kg i.v., ≤15 mg/kg p.o. or intraduodenal administration of ≤10 mg/kg. Unfortunately, average

Cmax values are only available following i.v. bolus injection of 0.02 mg/kg iloperidone (63 ng/ml ± 24 ng/ml) compared to slow i.v. infusion (15 ng/ml ± 8 ng/ml). Taking the iloperidone molecular weight of 426.5 g/mol into account, the plasma concentration of 63 ng/ml corresponds to a maximum exposure of about 150 nM. With regard to 86 % protein-binding in dogs, this culminates in a free plasma concentration of 21 nM. Likewise, no ECG findings were apparent in a 12 month chronic toxicity study in dogs with oral iloperidone doses up to 24 mg/kg/d corresponding to average exposure levels of ~30 ng/ml in males and ~120 ng/ml in females, i.e. free plasma concentrations of ~10 nM and 39 nM, respectively.

A retrospective analysis of literature hERG data indicated that block of hERG currents is associated with TdP arrhythmias if it occurs at concentrations close to those achieved in clinical use, and a 30-fold margin between free therapeutic plasma concentrations and IC50 values for block of hERG currents appears to be a line of demarcation between the majority of drugs associated with TdP arrhythmias and those which are not (Redfern et al. 2003). The IC50 values of iloperidone and the P88 metabolite for hERG currents are only 3.7- and 7-fold, respectively, higher when compared to the maximally therapeutic free plasma concentrations in the presence of CYP inhibition and 7.8- and 15-fold, respectively, higher when compared to the maximally therapeutic free plasma concentrations in the absence of CYP inhibition.

For drugs with mixed ion channel activity, the concentrations required for prolongation of the APD and the QT interval are dissociated from those blocking hERG channels/IKr, and their effects on other cardiac ion channels (Na+ and L-type Ca2+ channels) antagonize the effects of inhibition of IKr on APD and QT interval. Therefore, inhibition of inward plateau currents (ICaL or INa) may be protective against Torsades de Pointes cardiac arrhythmias. Remarkably, iloperidone and its P88 metabolite reveal effects on the action potential duration of dog ventricular Purkinje fibres that are characteristic for a pure K+ channel blocking agent.

Iloperidone and its P88 metabolite revealed higher affinity for the HERG channel than other antipsychotic agents and concentration-dependently prolonged APD durations in dog Purkinje fibres with characteristics of a pure K^+ channel inhibitor. These findings of a pronounced arrhythmogenic potential of iloperidone and P88 are in concordance with remarkable QT interval prolongations seen in a thorough QT study in patients, incidences of sudden death related to cardiac events in clinical trials and post-marketing and need to be further addressed clinically (see clinical AR). The absence of ECG findings in several *in vivo* studies in dogs can most probably be attributed to insufficient exposure of the study animals to iloperidone in these studies. it seems very questionable if the newly proposed dose reduction in clinical therapy will make the arrhythmogenic risk associated with iloperidone manageable in an ambulant setting, because a substantial risk of overdosing, for drug interactions at CYP2D6 and CYP3A4 and in highly vulnerable patients harbouring genetic mutations (e.g. hereditary long QT syndrome) remains.

Iloperidone is rapidly absorbed, extensively metabolised, widely distributed, and rapidly excreted mainly via faeces. Species differences in the metabolism compared to humans was observed.

A standard toxicological programme was conducted on iloperidone and the major human metabolite P95 was tested in a separate set of studies including repeat-dose toxicity, genotoxicity and carcinogenicity in the rat. Both iloperidone and P95 were devoid of any genotoxicity potential and most of the toxicity seen in the repeat-dose toxicity and carcinogenicity studies could be attributed to increased prolactin levels. Iloperidone had no effect on male fertility, was non-teratogenic, but had some effects on female reproduction, fetal and neonatal development. P95 did not cause any embryo-fetal toxicity when administered orally to pregnant rats.

Major deficiencies were noted in the 52-week study in dogs regarding the inappropriate iloperidone exposure of study animals and in terms of the presentation of the corresponding toxicokinetic data and

effects in the study report and in the summaries. Apart from central nervous system related clinical signs, the drug related effects were sparse and mainly mild in nature. It is therefore questioned whether the MTD was reached in this study. The toxicokinetic data indicated low or non-existent exposure in most of the dogs.

2.3.18. Conclusion on the non-clinical aspects

Apart from the still required appropriate environmental risk assessment in accordance with prevailing guidance, most concerns have been resolved or, at least, further elucidated by the Applicant. A close evaluation of toxicokinetic data from the pivotal chronic toxicity study in dogs revealed that animals were insufficiently exposed to iloperidone, which severely compromises the value of the study results for human risk assessment and most probably accounts for the absence of any arrhythmogenic effects of the compound in these animals. With respect to the inadequate toxicology program, any further risk assessment needs to be pursued clinically. From a preclinical perspective, marketing authorisation of iloperidone can therefore not be recommended in the light of the arrhythmogenic potential of the compound as a pure K^+ channel blocking agent.

2.4. Clinical aspects

2.4.1. Introduction

- Tabular overview of clinical studies

Study Identifier	**Study Objective**	**Study Design**	**Test Product and Dosing Regimen**	**Number of Patients /subjects**	**Duration of Treat-ment**	**Primary Parameter** (Change from baseline to endpoint)	**Study Locations (Countries)**
Bioavailability Studies							
ILPB103	Effect iloperidone and of food and PK	OL, co.	capsules, 3 mg, 2 single dose, oral	24 (healthy subj.)	2 single d., separated by 7 d wash-out	N/A	Canada
ILO522 0105	Compare PK + BA of ILO under fed/fasted cond.	R, OL, co.	tablet, 1 mg, 3 doses, oral and 3ml solution, 3 mg, single dose, oral	26 (healthy subj.)	Single 3 mg doses, 3 times 7 days apart	N/A	USA
ILO522 0104	PK of single d. ILO and to evaluate inter-action of ILO with a CYP P450 2D6-prototype substrate (dextro-methorphan)	R, OL, co.	<u>iloperidone:</u> Capsules, 3mg, 2 doses, oral <u>dextromethor-phan:</u> Elixir, 80mg, 2 single d.,oral	27 (healthy subj.)	1-2 days	N/A	USA
VP-VYV-683-1001	Compare BA of ILO immediate release to controlled release formulation	R, OL, co.	Capsule, 3mg, single dose, oral	16 (healthy subj.)	3 single d., separated by 7-10 days	N/A	USA
VP-VYV-683-1002	Compare BA of ILO tablets to over-encapsu-lated tablets	R, OL, co.	Iloperidone: Tablet, (3) 1 mg, single d., oral. (3) 1 mg tablets, over encapsulated, single d., oral	24 (healthy subj.)	1 single d. separated by 7-10 days	N/A	Switzerland
Bioequivalence Studies							

Study Identifier	Study Objective	Study Design	Test Product and Dosing Regimen	Number of Patients /subjects	Duration of Treat-ment	Primary Parameter (Change from baseline to endpoint)	Study Locations (Countries)
ILPB106	BE of ILO Capsule vs. Tablet	R, OL, co.	Tablet, 1mg, 2 doses, oral and Capsule, 1 mg, 2 doses, oral	30 (healthy subj.)	4 single d. separated by 7-10 days	N/A	USA
ILO522 0110	BE of 3 low strengths formulations of iloperidone	R, OL, co.	Over-encapsulated tablets, 1 mg, 3 doses, oral	24 (healthy subj.)	3 single 3 mg doses separated 7 days	N/A	USA
Pharmakokinetic Studies							
ILPB101/101 A	PK of single dose of ILO	DB, R, placebo, sequential	Capsules, 1,3 and 5 mg, single d., oral and matching placebo capsules, oral	27 (healthy subj.)	single dose	N/A	Canada
ILPB102	PK and Tolerability of Single d. of ILO	OL	2 mg, oral, single-d.	6 (healthy subj.)	single dose	N/A	Germany
ILPB105	PK and ADME of single d. of iloperidone	OL	Capsules, radio-labelled, 2.96 mg, oral, single dose	3 (healthy subj.)	single dose	N/A	UK
ILO522 2301	ADME of single dose of iloperidone	OL	Solution, radio-labelled, 3 mg, oral	6 (healthy subj.)	single dose	N/A	USA
ILPB203	Safety/tolerance study to determine the max. tolerated dose and titration schedule	OL, sequential-cohort	iloperidone: oral, capsules, up to 32 mg/d	24 (Hospitalized patients with chronic schizophrenia (all smokers))	up to 29 days	N/A	USA
ILO522 0112	PK of dose proportionality of iloperidone	OL	Tablets, 1 mg, multiple dose, oral	32 (Patients with schizophrenia)	41 days	N/A	USA
ILPB200	PK of multiple d. of ILO and its metabolites	DB, R, placebo	Capsule, 2-8 mg, multiple d., oral and matching placebo capsules, oral	18 (Hospitalized patients with schizophrenia)	28 days	N/A	USA
ILPB201	Safety and PK of titration schedule of iloperidone up to 16mg dose	DB, R, placebo	Capsules, 1-16 mg, mult.-d., oral and matching placebo	38 (Hospitalized schizophrenic patients)	28 days	N/A	USA
ILO522 B210	Safety and PK of two iloperidone depot variants	DB, placebo, parallel-gr.	iloperidone: tablets, 1mg and 4mg oral. Iloperidone suspended in 2-4 mLs of a vehicle solution: single IM injection	98 (Patients with schizophrenia)	21 days oral	N/A	USA
ILO522 0102	PK of single dose of iloperidone	OL, parallel-gr.	Capsule, (3)1 mg, single dose, oral	23 (Patients with chronic renal failure)	single dose	N/A	USA

Study Identifier	**Study Objective**	**Study Design**	**Test Product and Dosing Regimen**	**Number of Patients /subjects**	**Duration of Treat-ment**	**Primary Parameter** (Change from baseline to endpoint)	**Study Locations (Countries)**
ILO522 0103	PK of single dose of iloperidone	OL, parallel-gr.	Over-encapsulated tablets, 2mg, single dose, oral	16 (Patients with moderate hepatic impairment)	single dose	N/A	USA
ILO522 0104	PK of single d. of ILO and to evaluate interaction of ILO with a CYP P450 2D6-prototype substrate (dextro-methorphan)	R, OL, co.	Iloperidone: Capsules, 3 mg, 2 doses, oral Dextromethorphan: Elixir, 80 mg, 2 single doses, oral	27 (healthy subj.)	1-2 days	N/A	USA
ILO522 0107	PK of single d. of ILO and single d. ILO in combination with multiple-dose ketoconazole (a potent cytochrome P450 3A4 inhibitor)	R, OL, co.	Iloperidone: Tablets, 3 mg, 2 doses, oral Ketoconazole: tablets, 200 mg, 8 doses	19 (healthy subj.)	2 days	N/A	USA
ILO522 0108	PK of ILO in combination with fluoxetine	OL, co.	Iloperidone: Tablets, 3 mg, single d., oral Fluoxetine: capsules, 20 mg, multiple-d., oral	23 (healthy subj.)	27 days	N/A	USA
ILO522A 0109	PK of iloperidone in combination with valproate	OL, co.	Iloperidone: Tablets, 1 and 4 mg, multiple doses, oral Depakote® delayed-release tablets: 250 mg and 500 mg, oral	32 (Patients with schizophrenia)	25 days	N/A	USA

Study Identifier	Study Objective	Study Design	Test Product and Dosing Regimen	Number of Patients /subjects	Duration of Treat-ment	Primary Parameter (Change from baseline to endpoint)	Study Locations (Countries)
Pharmacodynamic Studies							
ILP3000	To characterize the population PK of ILO at steady state following multiple oral doses and to assess the the relationship between steady-state plasma conc. of ILO and its metabolite(s) and selected safety and efficacy variables in patients with schizophrenia and schizoaffective disorder.	R, placebo- and active controlled	iloperidone: oral, over-encapsulated tablets, 4 mg/d given as 6 mg BID, 8 mg mg/d given 4 mg BID, or 12 mg/d given as 6 mg BID. haloperidol: oral, over-encapsulated tablets, 15 mg/d given as 7.5 mg BID.	621 (121 ILO 4 mg/d; 125 ILO 8 mg/d; 124 ILO 12 mg/d; 124 haloperidol; 127 placebo) Patients with schizophrenia or schizoaffective disorder	6 weeks	N/A	USA
ILP3005	To characterize the population PK of ILO at steady state following multiple oral doses and to assess the the relationship between steady-state plasma concentrations of iloperidone and its metabolite(s) and selected safety and efficacy variables in patients with schizophrenia and schizoaffective disorder.	R, placebo- and active controlled	iloperidone: oral, tablets, 12-16 mg/d given as 6-8 mg BID, 20-24 mg mg/d given 10-12 mg BID. risperidone: oral, capsules, 6-8 mg/d given as 3-4 mg BID.	706 (244 iloperidone 12-16 mg/d; 145 iloperidone 20-24 mg/d; 157 risperidone 6-8 mg/d; 160 placebo) Patients with schizophrenia or schizoaffective disorder	6 weeks	N/A	U.S.A., Canada, Croatia, Germany, Hungary, Poland, Israel, South Africa
Dose-Finding Studies							
ILPB202 (Phase II)	Efficacy/ safety; schizophrenia	DB, R, placebo, 2 fixed doses	iloperidone capsules (HP 873), 4 mg/d or 8 mg/d vs. placebo; Application BID	Randomized Total: 104 ILO 4: 34 ILO 8: 34 Placebo: 35	Double-Blind 42 days	PANSS-T (Positive and Negative Syndrome Scale)	U.S.A.
Additional Efficacy / Safety Studies							

Study Identifier	**Study Objective**	**Study Design**	**Test Product and Dosing Regimen**	**Number of Patients /subjects**	**Duration of Treat-ment**	**Primary Parameter** (Change from baseline to endpoint)	**Study Locations (Countries)**
ILP2001ST	Short-term; Efficacy and safety; Comparison of titration schedules	DB, R, active controlled	ILO-oet 12 mg/d Application BID HAL-oet 15 mg/d , Appl. BID	Total: 120 ILO: 95 HAL: 25	6 weeks	PANSS-T	USA
ILP2001LT	Long-term; Efficacy and safety;	active controlled	ILO-oet 12 mg/d Application BID HAL-oet 15 mg/d , Appl. BID	Total: 23 ILO: 17 HAL: 6	98 weeks (mean 47.5 weeks)	PANSS-T	USA

Study Identifier	**Study Objective**	**Study Design**	**Test Product and Dosing Regimen**	**Number of Patients /subjects**	**Duration of Treat-ment**	**Primary Parameter** (Change from baseline to endpoint)	**Study Locations (Countries)**
Pivotal Studies							
ILP3000 (Phase III)	Efficacy/ safety of ILO (3 fixed dose) and HAL vs. placebo; schizophrenia /schizo-affective dis. with acute or subacute exacerbation	DB, R, placebo, active co., 3 fixed doses	Short-term: ILO-oet 4 mg/d 8 mg/d or 12 mg/d; Appl. BID HAL-oet 15 mg/d , Appl. BID Long-term: ILO-oet 4-16 mg/d once daily HAL-oet 5-20mg/d once daily	Randomized Total: 621 ILO 4: 121 ILO 8: 125 ILO 12: 124 HAL 15: 124 Placebo: 127 Schizophrenia 69% (428)	DB-Short-Term 6 weeks DB-Long-Term 46 weeks Open Label Extension with ILO Up to 3 years	PANSS-T (week 6)	U.S.A.
ILP3004 (Phase III)	Efficacy and safety of ILO (2 dose ranges) and RIS vs. placebo; schizophrenia/schizo-affect. disorder with an acute or subacute exacerbation	DB, R, placebo, active co., flexible dose range	Short-term: ILO -oet 4-8 mg/d or 10-16 mg/d; Appl. BID RIS capsules, 4-8 mg/d; Appl. BID Long-term: ILO-oet 4-16 mg/d once daily RIS capsules 2-8 mg/d once daily	Randomized Total: 616 Placebo: 156 ILO 4-8: 153 ILO 10-16: 154 RIS: 153 Schizophrenia 78% (499)	DB-Short-Term 6 weeks DB-Long-Term 46 weeks Open Label Extension with ILO Up to 2 years	BPRS (week 6)	U.S.A., Australia, Belgium, Canada, France, Hungary and South Africa

Study Identifier	**Study Objective**	**Study Design**	**Test Product and Dosing Regimen**	**Number of Patients /subjects**	**Duration of Treat-ment**	**Primary Parameter** (Change from baseline to endpoint)	**Study Locations (Countries)**
ILP3005 (Phase III)	Efficacy / safety of ILO and RIS vs. placebo; schizophrenia /schizo-affect. disorder	DB, R, placebo, active co.. 2 flexible dose ranges	Short-term: ILO tablets, 12-16 mg/d or 20-24mg/d; Appl. BID RIS capsules, 6-8 mg/d; Appl. BID Long-term: ILO tablets, 4-24 mg/d once daily	Randomized Total: 706 Placebo: 160 ILO 12-16: 244 ILO 20-24: 145 RIS: 157 Schizophrenia 78% (548)	DB-Short-Term 6 weeks Open Label Extension with ILO Up to 2 years	BPRS (week 6)	U.S.A, Canada, Croatia, Germany, Hungary, Israel, Poland and South Africa
VP-VYV-683-3101 (Phase III)	1) efficacy/safety 2) efficacy of ILO vs. placebo each in schizophrenic patients lacking the ciliary neurotrophic factor (CNTF) FS63Ter poly-morphism	DB, R, placebo, active co., fixed dose	Short-term: ILO-oet 24 mg/d, Appl. BID Ziprasidone-oec 160 mg/d, Appl. BID Open label: ILO-oet 12 mg/d, once daily or 24 mg/d Appl. BID	Randomized Total: 606 ILO 24: 303 ZIP: 151 Placebo: 152 Schizophrenia 100%	DB-Short-Term 4 weeks Open Label Extension with ILO Up to 26 weeks	PANSS-T (week 4)	U.S.A. and India
Long-Term Studies 3001-3003 (had the same study design, dose and endpoint)							

Study Identifier	**Study Objective**	**Study Design**	**Test Product and Dosing Regimen**	**Number of Patients /subjects**	**Duration of Treat-ment**	**Primary Parameter** (Change from baseline to endpoint)	**Study Locations (Countries)**
ILP3001 (Phase III)	efficacy / safety of ILO vs. HAL; schizophrenia / schizo-affective disorder	DB, R, active co., flexible dose range	ILO-oet 4-16 mg/d, Appl. BID HAL-oet 5-20 mg/d, Appl BID	Randomized Total: 600 ILO: 454 HAL: 146 Schizophrenia 92% (552)	Placebo-run in (day -2 to 0) DB-Short-Term 6 weeks (day 1 to 42) DB-Long-Term 46 weeks (day 43 to 364) Open-Label Extension with ILO Up to 2.5 years	See Meta ILP3001-3 PANSS-T (week 52)	Austria, Czech Republic, France, Germany, Hungary, Israel, Poland, and Switzerland
ILP3002 (Phase III)	efficacy / safety of ILO vs. HAL; schizophrenia / schizo-affective disorder	DB, R, active co., flexible dose range	ILO-oet 4-16 mg/d, Appl. BID HAL-oet 5-20 mg/d, Appl. BID	Randomized Total: 557 ILO: 420 HAL: 137 Schizophrenia 76% (421)	see study 3001	See Meta ILP3001-3 PANSS-T (week 52)	Egypt, Hong Kong, Indonesia, Malaysia, the Philippines Singapore, Taiwan, and Thailand
ILP3003 (Phase III)	Efficacy /safety of ILO vs. HAL; schizophrenia /schizo-affect. disorder	DB, R, active co., flexible dose range	ILO-oet 4-16 mg/d , Appl. BID HAL-oet 5-20 mg/d, Appl. BID	Randomized Total: 487 ILO: 365 HAL: 122 Schizophrenia 97% (473)	see study 3001	See Meta ILP3001-3 PANSS-T (week 52)	Argentina, Brazil, Chile, Colombia, and Mexico
Meta ILP3001-3 (Phase III)	maintenance effect of ILO vs. HAL; schizophrenia/ schizo-affective disorder over 46 weeks of treatment (pooled analysis from studies 3001, 3002 and 3003).	DB, R, active co., flexible dose range	ILO-oet 4-16 mg/d Appl. BID HAL-oet 5-20 mg/d Appl. BID	Randomized Total: 1644 ILO: 1239 HAL: 405 Schizophrenia Patients in the Analysis Population for long-term maintenance Total: 443 ILO: 337 HAL: 106	see study 3001 DB-Long-Term 46 weeks	Time to relapse	Pooled analyses! Population see above

HAL=haloperidol; ILO=iloperidone; RIS=risperidone; ZIP=ziprasidone

ILO-oet= iloperidone over-encapsulated tablets

Ziprasidone-oec = Ziprasidone over-encapsulated capsules

DB= double-blind; R= randomized; Appl.= Application; BID = twice daily

2.4.2. Pharmacokinetics

In total, 16 phase I trials, in a total of 341 subjects, have been completed to investigate the clinical pharmacology of iloperidone. Of these subjects, 273 subjects were healthy, 8 subjects had liver impairment and 10 subjects had renal impairment. 50 subjects were diagnosed with schizophrenia or schizoaffective disorder. The actually intended therapeutic dose range with this formulation is between 6 mg and 8 mg administered twice daily. In CYP2D6 poor metabilisers, a maximum dose of 6 mg twice daily is recommended.

Standard pharmacokinetic and statistical methods were used.

The analytical methods were overall acceptable. S-P88 is chiral, however no R-88 was detected in a chiral analysis method and hence it is acceptable that the analysis methods used are non-chiral.

Bioequivalence between the final marketing formulation and the formulation used in pivotal phase III studies, FMF-C, was established.

Absorption

In a food interaction study, a decrease in the rate of absorption was observed. Based on clinical safety data, it was observed that there were more adverse events in fasted conditions. Therefore, it may be more appropriate to administer the product in fed conditions. Given the results of the food interaction studies, it is clear that with the IR formulation, the number of gastrointestinal adverse events is clearly higher without food compared to with food (see study VP-VYV-683-1001). The following statement is given in the safety summary: “The incidence of adverse events was higher in fasted subjects compared with fed subjects who received the immediate-release formulation of iloperidone. In particular, nausea, dizziness, headache and somnolence occurred more frequently, and were more severe, in fasted subjects. The occurrence of adverse events was ameliorated by use of a controlled-release formulation, irrespective of food. Thus, the sponsor concluded that iloperidone could be safely administered with or without food, although tolerability of the immediate-release formula was better when iloperidone was taken with food.”

The Caco-2 cell study is indicative of active uptake, since there was a high AP to BL rate. Given the study design of the Caco-2 cell study, influence of protein and pH on AP to BL rate could not be concluded upon. Roughly linear pharmacokinetics prevails within the therapeutic dose range, and the influence of active uptake is likely limited.

The two Caco-2 cell studies show somewhat different results, however it is no clear signal that iloperidone, P88 or P95 are substrates of an efflux transporter.

Distribution

The volume of distribution has not been determined for iloperidone since no intravenous formulation has been administered. Based on estimated bioavailability of 54 % and 36 % in CYP2D6 EM and PM subjects respectively, the volume of distribution was approximately 700 L. Figures on the estimated bioavailability should be interpreted with caution, since there is a signal of gut metabolism of at least one major metabolite (P36.3). The mean protein binding was 95 % and somewhat lower in renal and hepatic impairment.

There is no information on the protein binding of the metaboliteP88. The recommended dose adjustments in special populations and with respect to interactions (slow metabolisers, concomitant administration of CYP3A4/CYP2D6 inhibitors) may have to be changed if the protein binding differs. The applicant has provided a response stating that it is unlikely that the protein binding differs between iloperidone and P88. However, also very similar molecules can show differences in the protein binding. Further investigation of the protein binding of both iloperidone and P88 in the same in vitro system is needed.

Elimination

The major route of elimination is metabolism in the liver in both CYP2D6 EM and PM subjects and excretion takes place mainly in the urine (various metabolites, where P95 is the dominant one, but also S-P88 (active) and P17.6, P20.8, P36.3 (open ring) and phenol and a glucuronide of P95 contributes. The active metabolite, P88 constitutes approximately 5-7 % of the dose in urine. P95 constitutes between 7 and 17% in CYP2D6 PM and EM subjects respectively. The P95 glucuronide metabolite is also excreted in faeces, approximately 6 % in both EM and PM subjects. Approximately 60 % and 12 % of the total 72 % identified of the dose is excreted in urine and faeces respectively and the total recovery near 90 %. Approximately 0.75 % is excreted as unchanged iloperidone in urine, none is observed in faeces.

The applicant performed a mass-balance study with a low amount identified in plasma out of the total radioactivity, 22 % of the radioactivity could be extracted. A very-long elimination half-life of total radioactivity compared to extracted radioactivity of approximately 150 hours compared to 32 hours was observed. Since the radioactive recovery in urine and faeces was almost complete, near 90 %, the remaining amount is likely related to a small but slowly eliminated entity. The applicant claimed that the remaining radioactivity constituted a two-carbon entity, acetaldehyde that was incorporated into macromolecules being part of the citric acid cycle.

The applicant was asked to improve the justification that the remaining activity with a very long elimination half-life could be attributed to acetic acid and/or acetaldehyde. The applicant was also asked to discuss if other polar metabolites may have been missed or if any other reason can explain the observation. The applicant has responded that it is likely that the remaining amount is acetaldehyde but cannot exclude other polar metabolites. The percentage exposure of iloperidone compared with the total radioactivity is similar in mouse and human, whereas the ratio is somewhat higher in dogs and rabbits. The ratio of elimination half-lives of iloperidone to the half-life of total radioactivity is also similar in human and rabbits, and comparable between humans and dogs. The percentage of total radioactivity extracted is not available from the animals; therefore this comparison cannot be made. The applicant agrees that there may be unidentified metabolites in human plasma, but puts focus on the safety data available, in the registration file and for 2 years of post-marketing in the US. The argument of incorporation of acetaldehyde in the citric acid cycle following metabolism of iloperidone could not be fully substantiated but this comparison of data indicates that there are similarities between the species, in that iloperidone elimination half-life is short in comparison to the overall half-life of radioactivity, supporting that incorporation of acetaldehyde is a likely mechanism for the low percentage of radioactivity extracted.

Iloperidone is metabolised via several pathways. CYP2D6 catalyse the formation of P95 from P94. The enzyme catalysing iloperidone to P94 is likely CYP2D6. Carbonyl reduction via carbonyl reductase is responsible for the formation of S-P88, and the reaction is reversible. CYP3A4 catalyses the formation of the P89 metabolite but is not an important pathway as stated by the applicant since such a low amount of P89 and its further glucuronide is formed. It seems as if the formation of P36.3 and P20.8 is more important compared to the formation of P89. Based on the in vitro study R01 538, CYP3A4

seems responsible for the formation of P20.8 but there is no presentation of the enzyme responsible for the formation of P36.3 (including the open ring). Given that the P36.3 pathway is not that large (based on excretion in urine and faeces); it is acceptable that the applicant has not determined the enzyme catalysing this pathway.

There is a large contribution by the metabolites to the total exposure, approximately 1.5-fold for S-P88 and 2.5-fold for P95 compared to iloperidone in CYP2D6 EM subjects. In CYP2D6 PM subjects, the contribution of P88 is 2-fold over iloperidone and P95 0.7-fold. P95 is likely not active. However, with respect to safety, it cannot be ruled out that P95 could have an effect, e.g. in patients with severe renal impairment and several fold increase in the exposure.

Iloperidone is metabolised by CYP2D6 and this enzyme system is known for its genetic polymorphism. Although the genotyping have not been described in detail and only 2 alleles have been accounted for, it can be concluded that these groups show deviating pharmacokinetic profiles. In poor metabolisers iloperidone and P88 are significantly increased (AUC0-∞ by 57% and 95%, respectively) whereas the exposure of P95 decreased (AUC0-∞ by 80%).

The applicant states that the active moiety is approximately 152 % increased (based on increase of iloperidone (57 %) and P88 (95 % increased) in CYP2D6 PM subjects compared to EM subjects and and that a dose reduction is needed for CYP2D6 EM subjects. The current proposal in CYP2D6 EM subjects is a maximum dose of 16 mg; therefore a maximum recommended dose of 8 mg in CYP2D6 PM subjects should be recommended, since there is a dose-dependent increase in QTc and this would be in line with the recommendation regarding administration with a strong CYP2D6 inhibitor. A QTcF correlated to the various alleles (*4/*4, *4/*10 and others) would have provided more insight what the most appropriate dose in each group of various metabolising capacity would be. There is an increase in half-life of P88, supporting that P88 may be metabolised further via CYP2D6. The applicant has discussed the proposed dose adjustment in CYP2D6 PM subjects given the difference in pharmacokinetics compared to CYP2D6 EM subjects. Given that P95 can be considered in principle inactive, the two-fold reduction in dose can be considered to be acceptable.

The applicant was asked to provide a justification that the thorough QT-study is representative for a patient being CYP2D6 poor metaboliser administered a potent CYP3A4 inhibitor. The QT study would be expected to be representative of a CYP2D6 poor metaboliser administered a strong CYP3A4 inhibitor, however the QT results of the pharmacogenetic substudy of the QT study show that the QT relative difference is larger in subjects being CYP2D6 poor metabolisers compared to CYP2D6 metabolic inhibition. In addition, there are other strong CYP3A4 inhibitors with longer half-life, such as itraconazole, that could exert a larger interaction effect on iloperidone.

The applicant is further asked whether genotyping is a way forward in CYP2D6 poor metabolisers to minimise the risk in patients being CYP2D6 poor metabolisers. The applicant has responded and propsed genotyping for CYP2D6 if the dose is intended to be higher than 6 mg twice daily. Given the exposure difference, it would be logical to perform genotyping of CYP2D6 at a maximum dose of 8 mg daily, given that the maximum dose in subjects being CYP2D6 EM subjects is 16 mg. There is another polymorphic gene, KCNQ1 that is of importance. With the current SmPC proposals, a safe use cannot be assured. The proposal by the CHMP is to lower the dose for which genotyping should be made to 8 mg, to recommend avoiding the use of strong CYP2D6/CYP3A4 inhibitors. In addition, genotyping of KCNQ1 seem of high importance, given its association with prolonged QTc interval for mutant alleles, with a larger effect on QTc interval than what is observed with CYP2D6 poor metabolism/CYP2D6 strong inhibitors. In study 3101 the relationship to KCNQ1 could not be confirmed.

Dose proportionality and time dependencies

For iloperidone, dose-proportionality was concluded in the dose range of 1 mg BID to 8 mg BID. For a dose of 12 mg BID a small deviation from dose proportionality for iloperidone is shown. Dose proportionality is shown for P95 and P88 in the iloperidone dose range of 2 mg BID to 12 mg BID. Phase 3 data obtained at steady state was reasonably well described by the population PK model developed based on phase 1 data estimated based on single dose administration data. This supports that pharmacokinetic features are independent of time but does not constitute a thorough evidence of lack of time dependency.

The unexplained inter-individual variability for apparent clearances of iloperidone, P88 and P95 were 39%, 44% and 47%, respectively, in the final population PK model based on study VP-VYV-683-3101. Since the estimate of the variability of CL/F is following inclusion of covariates (including CYP2D6 polymorphism) in the model this is an underestimation of the overall inter-individual variability.

Special populations

In patients with severe renal impairment, the exposure of iloperidone was increased approximately 1.5-fold (based on AUC0-∞), P88 was decreased to approximately 0.7-fold and P95 significantly increased with mean values up to 3-fold, and individually up to 4-fold, if based on AUC0-∞. Even though the actual magnitude of the P95 exposure increase is not well estimated given a large extrapolation in many of the subjects with renal impairment due to the markedly prolonged elimination half-life, it is clear that a marked exposure increase is reached. The applicant does not recommend any dose adjustment although iloperidone exposure is increased and P95 is significantly increased. With the applicant's response, it is still unknown what the consequences are of an highly increased P95 exposure.

Based on the plots of exposure of iloperidone (unbound), P88 and P95 vs. individual creatinine clearances provided, there are significant increases in exposure of iloperidone, P88 and P95 in the group of severe renal impairment.

The metabolism of iloperidone involves both CYP enzymes and carbonyl reductase. As a mean between the mild and moderate hepatic impairment groups, the exposure of P88 is increased 1.6-fold, the point estimate of iloperidone is not significantly higher (15-20%) and P95 also shows comparable or somewhat lower exposure. The applicant claims that this may be due to extrahepatic metabolism of the carbonyl reduction (related to the increased formation of P88) and the reduced formation of P95 being related to reduced capacity of CYP2D6 in hepatically impaired subjects. The applicant was asked to present data separated on mild and moderate hepatic impairment (unbound for iloperidone). In the CHMP´s opinion, the low exposure increase observed for iloperidone could be due to that a decrease in CL is masked by an increase in the free fraction in plasma. The applicant did not present the data, instead a new study will be performed in patients with hepatic impairment, planned to be completed with study report in June/July 2012. The applicant has proposed that use in subjects with hepatic impairment be contraindicated until the results of the new study are available.

Based on the renal clearance figures presented, P88 and P95 may be actively secreted. The applicant has however not determined the protein binding of the metabolites and therefore filtration cannot be calculated with the current available information. The applicant has not determined the protein binding of P88 but is asked to determine this as a post-approval measure. When calculating the contribution of renal clearance to total clearance of P88 and P95, it can be concluded that P88 does likely not have a sufficiently large renal elimination that would make it clinically relevant. Therefore, further determination of a transporter responsible for active secretion is not requested. P95 may have a significant active renal secretion when comparing the amount excreted as P95 in the urine with the

amount further metabolised. However, given the activity of this metabolite considered to be in principle inactive, determination of active secretion transporter(s) is not asked for.

For both the renal and hepatic impairment studies, safety conclusions that can be made from these studies are limited since the dose administered was low in comparison to the proposed therapeutic doses (up 12 mg BID, compared to 3 and 2 mg administered in the renal and hepatic impairment studies respectively). It is therefore recommended that use is contraindicated in severe renal impairment (including ESRD) and for patients with moderate renal impairment, caution is advised. Until results are available from the new hepatic impairment study, a contra-indication for patients with moderate and severe hepatic impairment is proposed by the applicant and agreed.

With respect to gender, race and weight, there was no statistical analysis based on the phase I studies. From the population pharmacokinetic analysis, analyses were undertaken investigating the effect of gender, race and weight. The bioavailability was estimated to be approximately 50 % higher in women.

However, there are uncertainties with the model, making the conclusion of a gender effect uncertain. It was observed that a doubling of weight was associated with a limited increase in the exposure of approximately 15 % and therefore not relevant for dose adjustments.

Shrinkage for post-hoc estimate of eta on clearance was reported to be moderate, 22%. Epsilon shrinkage was not reported. Even moderate shrinkage in eta and small shrinkage in epsilon can conceal model misspecification when performing graphical analysis of residuals.

There is no information on the pharmacokinetics in elderly above 75 years of age.

No data are available in the paediatric population. A product specific waiver was granted for paediatrics by the PDCO.

Pharmacokinetic interaction studies

The inhibition of CYP 1A2, 2C8, 2C9, 2C19, 2D6, 2E1 and 3A4/5 by iloperidone, P88 and P95 was evaluated using pooled human liver microsomes from 16 donors. There is no clinically relevant systemic inhibition of CYP3A4 and CYP2D6 by iloperidone, P88 or P95. The applicant was asked to discuss inhibition of CYP3A4 in the intestines, since inhibition of CYP3A4 is possible given the IC50 values observed and an intestinal concentration that may reach 12 mg/250ml= 0.048 mg/ml≈112 μ M). Since intestinal inhibition of CYP3A4 cannot be excluded, the applicant is asked to investigate inhibition of CYP3A4 in vivo with midazolam as substrate.

The induction potential of iloperidone, P88 and P95 were evaluated for 48 hours at three concentrations, 0.05, 1 and 20 µM using hepatocytes from three individual donors. The investigated enzymes were CYP1A2, CYP2C8, 2C9, 2C19 and CYP3A4/5. In the CYP in vitro induction study, inhibition is observed for CYP2C9, 2C19 and 3A4 and therefore mRNA should have been measured. There is also a weak induction signal for 2C8. The overall conclusion is that nothing can be concluded with respect to PXR regulated enzymes (possibly with the exception of CYP2C8). A new in vitro induction study evaluating the effect on 2B6 and 3A4, measuring mRNA and using 20 µM rifampicin as positive control, should be performed. The possibility of inducing effect on CYP3A4 could also be investigated in the midazolam in vivo interaction study (making sure the study duration is long enough to be representative of possible induction).

Iloperidone and P88 both inhibited the digoxin transport with complete inhibition showing an efflux ratio of 1. P95 did not inhibit digoxin transport to a relevant extent. When calculating the maximum dose/250 ml for potential intestinal inhibition of p-gp, the potential concentration is 0.048 mg/ml

(12mg/250 ml). This corresponds to approximately 112 µM, and the ratio between the iloperidone concentration and IC50 for inhibition of p-gp is 127-fold.

An in vivo study investigated the effect of ketoconazole 200 mg bid for four days on the pharmacokinetics of iloperidone, P88 and P95. The exposure increase of iloperidone in CYP2D6 extensive metabolisers was approximately 50 %. P88 and P95 increased by approximately 60 and 40 % respectively. The results are indicative of a parallel pathway catalysed by CYP3A4 (other than the one stated by the applicant to be related to P89). It is likely that inhibition of the formation of P20.8 (N-dealkyl iloperidone) via CYP3A4 is partly responsible for this exposure increase. There is a recommendation to reduce the dose by 50 % with concomitant administration of a strong CYP3A4 inhibitor. Although there is no specific support for the 50 % dose reduction, this will decrease the Cmax and therefore possibilities for QT-prolongation will be reduced. The resulting exposure of iloperidone after dose adjustment will be approximately 75 % compared to without a CYP3A4 inhibitor in a CYP2D6 EM subject.

Paroxetine and ketoconazole were co-administered with iloperidone 8 mg BID, 12 mg BID and 24 mg QD in a thorough QT study. The peak steady state concentrations of iloperidone, P88 and P95 were determined in the presence and absence of metabolic inhibition. The peak concentration of iloperidone increased upon co-administration with paroxetine and paroxetine/ketoconazole approximately 1.6- and 2.3-fold. The corresponding figures for P88 were 1.6-1.7 and 2.3-2.7-fold respectively. For P95, the corresponding figures were 0.5 and approximately 0.3 respectively. The fold-increase in peak concentrations is unexpectedly small but does not fully reflect the exposure, AUC that is expected to be increased to a larger extent.

The mean QT interval change from baseline increased with dose and with the concomitant administration of CYP3A4 and CYP2D6 inhibitors. The largest increases in concentration of iloperidone and P88 were observed in the iloperidone 8 mg BID and iloperidone 12 mg BID groups, which were also associated with the largest increases in QTcF from Treatment Period 1 (without inhibitor) to Treatment Period 3 (with CYP2D6 and CYP3A4 inhibitor). Seven patients in the iloperidone treatment arms experienced a change in QTc value of > 60 msec at Tmax. 10 patients had a QTc prolongation of more than 60 msec in the secondary analyses, approximately 10 % of patients who received iloperidone.

There is a higher risk of QTc prolongation in CYP2D6 poor metabolisers, and genotyping is even more critical if combined with a CYP3A4 inhibitor. The results of the pharmacogenetic substudy of the thorough QTc study shows that with respect to relative changes in QT, are larger in subjects being CYP2D6 poor metabolisers compared to QTc relative changes with strong metabolic inhibition of CYP3A4 and CYP2D6. This further strengthens the requirement to genotype for CYP2D6. In comparison to ziprasidone, the potential for QTc prolongation is higher based on a different interaction profile, since aldehyde oxidase catalyses the major metabolism pathway of ziprasidone, followed by CYP3A4, in contrast to the CYP2D6 metabolism pathway of iloperidone. The applicant was asked to discuss whether genotyping of CYP2D6 is a way forward in treating these patients and has now proposed a CYP2D6 genotyping programme. For CYP2D6 poor metabolisers the highest recommended dose should be lowered from 12 mg daily to a daily maximum dose of 8 mg. Based on the applicant´s response to questions, and data from study 3101 on KCNQ1, the applicant claims that there is no relationship between KCNQ1 and QT-prolongation for iloperidone. Importantly however, that polymorphism of this gene has been suggested to be associated with long QT syndrome in the literature. The statistical analysis to evaluate KCNQ1 polymorphism and QT-prolongation is also questionable.The exposure of iloperidone increased 2.2-fold upon co-administration of a potent CYP2D6 inhibitor and 2.1-fold for P88. For P95, the exposure upon co-administration was approximately 0.4-fold. The applicant recommends dose reduction to half the dose with fluoxetine and other strong CYP2D6 inhibitors. The exposure increase is somewhat larger with fluoxetine compared to the exposure increase in a subject

being CYP2D6 poor metaboliser. This may be due to that fluoxetine also inhibits CYP3A4 to some extent. The main reason for dose reduction is to decrease the risk of QT-prolongation. It is currently proposed that use with strong CYP2D6 inhibitors inhibitors is avoided. If it is not possible to avoid concomitant use, half the dose should be administered.

The effect of iloperidone 3 mg on CYP2D6 inhibition in vivo was an increased Cmax of 24 % and 10 % increases in AUC of dextromethorphan. The elimination half-life of the active metabolite to dextromethorphan, dextrorphan, was increased from 4.5 to 7.2 hours (+ 58 %). The dose of iloperidone, 3 mg, was low and dosing to steady state was not performed, therefore the effect may have been underestimated. Dextrorphan is metabolised further via CYP3A4. The increase in elimination half-life of dextrorphan is indicative of CYP3A4 inhibition in the liver.

Interactions with respect to active renal secretion are likely not relevant for P88 given the rather low contribution to renal elimination in comparison to its metabolism. For P95 active secretion may have a larger importance, however since it is accepted that P95 is inactive it is acceptable not to investigate the transporter possibly responsible for active secretion (if present).

The applicant has not investigated or addressed the potential for interactions at the biliary transporter level. Given the low percentage excreted in the faeces, clinically relevant biliar transporter interactions are likely not present.

The consequences for the exposure of iloperidone and metabolites in patients with a combination of poor metabolism and/or metabolic inhibition and renal impairment are unknown.

2.4.3. Pharmacodynamics

Mechanism of action

Iloperidone is a new chemical entity and belongs to the chemical class of piperidinyl-benzisoxazole derivatives developed for the treatment of schizophrenia in adults. Iloperidone has high (nM) affinity for $5HT_{2A}$-/$NE\alpha_1$-/$NE\alpha_{2C}$-/D_2/D_3/- and 5-HT_{1A} receptors in humans and acts as an antagonist at selected dopaminergic, serotoninergic, and adrenergic receptors. The mechanism of action, as with other atypical antipsychotics, is believed to be preferentially mediated through a combination of D_2-dopamine and serotonin 5-HT_{2A} receptor antagonism. Antagonism at receptors other than D_2 and $5HT_{2A}$ may explain some of the other effects of iloperidone.

Primary and Secondary pharmacology

Pharmacodynamic (PD) endpoints were evaluated in:

5 short-term (4-6 weeks) iloperidone efficacy and safety studies altogether including pivotal and supportive studies as follows:

- One supportive randomized Phase II (ILPB202) efficacy and safety study in patients with schizophrenia
- Four pivotal randomized, double blind, placebo-and active controlled Phase III efficacy and safety studies (Studies ILP3000 ST, ILP3004ST, ILP3005ST in patients with schizoaffective disorder or schizophrenia combined, and Study VP-VYY-683-3101 including patients with schizophrenia)
- Three main Phase III randomized and active-controlled supportive short-term and maintenance studies (Studies 3001, 3002, and 3003), in which the efficacy of iloperidone was compared

with the reference product haloperidol in controlling the acute psychotic symptoms in patients with schizoaffective disorder or schizophrenia

3 long-term (52 weeks) iloperidone maintenance of effect studies in patients with schizoaffective disorder or schizophrenia as follows:

- Studies ILP3001, ILP3002 and ILP3003 were identical (prospective, randomized, multi-center, double-blind, flexible-dose, parallel group), designed to evaluate the long-term efficacy and safety of iloperidone given at dosages of 4-16 mg/day as compared to the reference product haloperidol given at dosages of 5-20 mg/day over a 12-month period. The objective was to compare the two treatments in the prevention of relapse during the long-term phase of the study. Please find tabular listing of main clinical long-term studies below.

Furthermore, the PK/PD relationship to QT/QTc prolongation in patients with schizoaffective disorder or schizophrenia (Study ILO 522 2328), the efficacy based on Ciliary Neurotrophic Factor (CNTF) genotype (Study ILP 3005) and the CNTF FS63Ter polymorphism, has also been studied. Efficacy from four Phase III studies (3000, 3004, 4005 and 3101) were pooled and analyzed across trials (Study Meta ILP3001-3003 CSR).

It should be noted that 3 of the 5 short-term studies and all long-term studies included a mix of patients with schizophrenia *or* schizoaffective disorder, i.e. two diagnostic entities within the DSM-IV diagnostic system were applied in this application. Please find tabular listing of main clinical short- and long-term studies included in the following section.

2.4.4. Discussion on clinical pharmacology

The QTc changes as observed with this product are of concern. There are clear indications that the effect on QT is increasing with increased concentrations, especially for P88. The QTc changes are increased on mean levels up to 20 msec under full metabolic inhibition. In individual patients, changes above 30 and 60 msec have been observed. The applicant has proposed a genotyping programme for CYP2D6, to minimise the risk of QTc prolongation associated with increased exposure. The proposal is to genotype if the dose goes above a daily total dose of 12 mg. In CYP2D6 EM subjects, the proposal is to reduce the maximum daily dose from 24 mg to 16 mg. It is considered that there is still a need for further dose reduction in CYP2D6 PM subjects and genotyping should therefore be performed at a lower dose of 8 mg (total daily dose). The Applicant has however not fully investigated the full relationship between various allele combinations and QTcF-prolongation. A further deficiency is the method handling data by pooling results from CYP2D6 intermediate and poor metabolizers potentially diluting QTcF-prolongation data.

Use with other strong CYP2D6/CYP3A4 inhibitors should be avoided. If it is not possible to avoid concomitant administration of CYP2D6/CYP3A4 inhibitors, the dose should be reduced to half the previously administered dose.

With respect to the KCNQ1 gene, the originally reported significant prolongation related to KCNQ1 polymorphism could not be validated in a Whole Genome Polymorphism study 3101. However the statistical analysis to evaluate KCNQ1 polymorphism and QT-prolongation is questionable. When using hypothesis testing for evaluation of safety and tolerability, statistical adjustments for multiplicity to quantify the type I error are appropriate, but the type II error is usually of more concern.

The explanation for the discrepancy in the results of the genotype analysis of SNP [AJ006345.1 (797674] in the two association studies is not known. Genotype analysis was performed in a larger patient group in the validation study (183 patients) than in the thorough QT-study (67 patients), suggested as a plausible explanation by the Applicant. Since the initially reported results could not be

validated, the KCNQ1:CYP2D6 interaction test was not investigated. Given the support from the potential QT-prolongation effect of KCNQ1 and KCNH2, and the initially presented results, such an interaction analysis may provide support for an additional QT-prolongation effect following polymorphism of KCNQ1/KCNH2 and CYP2D6 in combination.

It can be concluded that safety of a combination of KCNQ1 and CYP2D6 is not clearly elucidated based on the data from study 3101. The safety concern with respect to KCNQ1 polymorphism and potential clinically relevant QTc-prolongation remains.

It is concluded that the metabolite P95 does likely not contribute to efficacy. In a population with severe renal impairment, it cannot be excluded that there are safety consequences with a several fold increase in the exposure of P95. The applicant has proposed further contraindications in patients with severe and end stage renal impairment, awaiting the results of a new renal impairment study that was proposed as a post-authorisation measure.

A further in vivo study is recommended in moderate and severe renal impairment and interaction studies to investigate the potential for inhibition by iloperidone on CYP3A4 in the intestines (study with oral midazolam). It was proposed to contraindicate all grades of hepatic impairment, awaiting the results of the hepatic impairment study.

The applicant was asked to clarify the metabolite pattern in plasma of all animals and compare it with the profile in humans, including a comparison of the elimination half-life of the total radioactivity. The comparison of human with animal data indicates that there are similarities between the species, in that iloperidone elimination half-life is short in comparison to the overall half-life of radioactivity, supporting that incorporation of acetaldehyde is a likely mechanism for the low percentage of radioactivity extracted.

2.4.5. Conclusions on clinical pharmacology

The absorption and distribution of iloperidone does not raise any specific concerns. A food interaction is not evident from pharmacokinetic data; however differences in the adverse events profile was observed, in favour of fed conditions. The metabolism is unfavourable in terms of elimination via CYP2D6. There are still uncertainties with respect to safety of P95 if the exposure is significantly increased, such as for patients with severe renal impairment.

An increased QTc prolongation potential is present in CYP2D6 poor metabolisers without further inhibition of the metabolism (with CYP3A4 inhibitors). Subpopulations at risk include patients being CYP2D6 PM subjects, patients administered CYP3A4 and CYP2D6 inhibitors, patients with renal and hepatic impairment, possibly female gender and patients administered other medicinal products with known QT interval prolongation properties.

A clear contra-indication in combination with other medicinal products with QT prolongation potential and in patients with hepatic impairment would be warranted given the observed individual QT changes and sudden death cases reported from the use of the product. The QT potential is still considered a major safety issue in patients being CYP2D6 poor metabolisers. The positive predictive value of decreasing exposure in subjects being CYP2D6 poor metabolisers in terms of decreasing the risk of QT prolongation and ultimately TdP is unclear. Still, based on the data presented so far, the safe use in patients being CYP2D6 poor metabolisers without performing CYP2D6 genotyping cannot be ascertained.

A further deficiency is the method handling data by pooling results from CYP2D6 intermediate and poor metabolizers potentially diluting QTcF-prolongation data.

Based on the thorough QT-study a significant and potentially clinical relevant QTcF-prolongation effect from KCNQ1 polymorphism was suggested. In a subsequent gene association study, no such effect could be validated. Since the initially reported results could not be validated, the KCNQ1:CYP2D6 interaction test was not investigated. Given the support from the potential QT-prolongation effect of KCNQ1 and KCNH2, and the initially presented results, such an interaction analysis may provide support for an additional QT-prolongation effect following polymorphism of KCNQ1/KCNH2 and CYP2D6 in combination. The explanation for the discrepancy in the results of the genotype analysis of SNP [AJ006345.1 (797674] in the two association studies is not known. The statistical analysis used in study 3101 is questionable. The safety concern with respect to KCNQ1 polymorphism and potential clinically relevant QTc-prolongation remains.

2.5. Clinical efficacy

2.5.1. Dose-response studies and main clinical studies

Short-term studies

Four pivotal placebo- and /or active-controlled short-term trials have been submitted (3101, 3000, 3004, 3005). In these trials a total of 2081 schizophrenic patients have been included. Duration of the studies resp. short-term phases of these studies were 6 or 4 weeks. Studies 3000 and 3004 were followed by a double-blind 46 weeks long-term phase.

Long-term studies

Long-term efficacy has been evaluated in three double-blind randomized studies in a total of 1446 schizophrenic patients (studies 3001, 3002, 3003). These studies had identical study design and duration was 52 weeks. In a pooled analysis of the three long-term studies time to relapse with iloperidone compared to haloperidol was evaluated.

All studies were followed by an open-label extension phase with iloperidone up to 3, 2.5, resp. 2 years or up to 26 weeks.
Most of the studies (apart from phase II study B202 and phase III short-term study 3101) included patients according to DSM-IV with schizophrenia [disorganized (295.10), catatonic (295.20), paranoid (295.30), residual (295.60 or undifferentiated (295.90) as well schizoaffective disorder (295.70)]. Due to this mixture of patients for most pivotal studies apart from short-term phase III study 3101 for the subpopulation of schizophrenic patients only post hoc analyses are available.

The dose-finding, pivotal studies and long-term studies are double-blind, randomized, placebo-controlled and/or active controlled.

In the former stages of assessment the Applicant claimed that iloperidone has been shown to be effective for treatment of schizophrenia in both the acute and long-term setting supporting a target dose of 12 to 24 mg/d in the acute setting and a dose of 12 mg/d for maintenance. Now actually for the acute setting the Applicant proposes a lower maximal dose, i.e. 12 to 16 mg/d to address the safety issues and for maintenance treatment he proposes as well 12 to 16mg/d. Given the safety concern on the QT-prolongating effects that have been confirmed including CYP2D6 – as well as KCNQ1-polymorphism and drug-drug inhibition following concomitant medication, the Applicant has presented a proposoal for risk minimisation and guidance on dose selection for iloperidone to account for the increased potential risk for cardiac arrhythmia.

Baseline Data

Pivotal short-term study 3101 is the only one with exclusively schizophrenic patients. The percentage of schizophrenic patients in short-term studies 3000, 3004 and 3005 was 69%-78%. In the HAL-compared long-term studies 3001, 3002 and 3003 also most of the patients had schizophrenia (92%, 76% resp. 97%). Most of he patients had a diagnosis of paranoid schizophrenia. Mean baseline PANSS was 94.4 – 97.0 (study 3000) and mean baseline BPRS 53.3 – 55.6, whereas in the long-term studies means baseline PANSS was a bit lower (89.4 to 93.2). According to S. Leucht et al. a PANSS of 95 points corresponds to a CGI severity score of "markedly illl' (*S. Leucht et al., What does the PANSS mean? Schizophrenia Research 2005; 79:231-238).* The patient population was predominantly male (68% up to 83% in short term studies) and some more balanced in the long-term studies (55% to 66% males). The age ranged from 17-69 years and average age was in the late thirties.

Baseline demographic and clinical characteristics were similar between treatment groups in each study.

Most patients in the pivotal studies came from USA, Asia, and South-America. Only in the pivotal studies 3004 and 3005 and long-term study 3001 some EU-patients were included. In study 3101 with exclusively schizophrenic patients most of the patients/centres were from USA and the other 8% from India.

Blinding

The pivotal short-term efficacy studies were all placebo-controlled, randomized and double-blinded as defined in the study design of each trial. The possible unblinding effect of differences in side-effect occurrence between iloperidone and active comparators trials on efficacy and safety, with a possible bias of validity, is discussed by the Applicant. It is argued that this unblinding effect may bias the validity especially at the early phase of the study when the occurrence of adverse events/side-effects could be expected to be characteristic for the comparator however low for iloperidone. This may generate higher drop-out rates for iloperidone since the delayed clinical effect due to the dose titration needed. The impact of this unintended unblinding is that bias is introduced, as referenced in ICH E10.

Treatments / Exposure to Study Drug

Three studies with fixed doses have been conducted (phase II study B202 and studies 3000 and 3101).

Dose-finding study: Application BID

B202: ILO 4 or 8 mg/d (capsules!) and placebo; fixed doses

Short-term studies: Application BID

3000: ILO 4, 8 or 12 mg/d, HAL 15mg/d and placebo; fixed doses
3004: ILO 4-8 mg/d or 10-16 mg/ d, RIS 4-8 mg/d and placebo
3005: ILO 12-16 mg/d or 20-24 mg/d, RIS 6-8 mg/d and placebo
3101: ILO 24 mg/d, ZIP 160 mg/d and placebo; fixed doses

Long-term-studies (including the initial 6 week phase): Application BID

These 52 weeks-long-term studies had an identical design (non-inferiority design, parallel groups, and flexible doses) comparing iloperidone 4-16 mg/day to haloperidol 5-20 mg/day. The objective was to compare the two treatments in the prevention of relapse during the long-term phase of the study via pooled analysis:

3001: ILO 4 -16 mg/ vs. HAL 5-20 mg/day day
3002: " "
3003: " "

In the long-term extension phases following the short-term studies a once daily regimen was used resp. in the long-term-extension phase following study 3101 the drug was applied once or twice daily.

Titration:
The short-term phases of all studies included a titration period of 7 days, starting with ILO 2mg/d, HAL and RIS 2mg/d resp. ZIP 40mg/d.

The table below provides the cumulative patient-years of exposure to study drug. Please note that approximately 45% of exposure occurred during open-label iloperidone treatment (997 patient years). Nearly half of the patients received a modal dose of iloperidone 10 to 16 mg/day, for a cumulative exposure of ~1245 patient-years at that dosage, Table 1.

Table E1: Cumulative Patient-Years of Exposure to Study Drug

Group	Number Treated	Cumulative Extent of Exposure (Patient-Years)
Placebo	587	41.71
Iloperidone	3297	2070.31
4-8 mg/day	1227	703.66
10-16 mg/day	1562	1254.58
20-24 mg/day	508	112.07
Haloperidol	546	261.57
Risperidone	311	56.30
Ziprasidone	184	10.09

Data Source: ISS Table 33.1.1, includes studies 2001, 3000, 3001, 3002, 3003, 3004, 3005, 3101, and period 1 of 2328.

Drug formulations used in clinical studies

Several formulations of iloperidone have been used in the clinical trials. In the phase II dose-finding study ILPB202 iloperidone capsules and in the pivotal study ILP3005 iloperidone tablets have been used. In all other pivotal studies over-encapsulated iloperidone tablets (in the table above "ILO-oet" stands for this formulation) have been applied. Nevertheless not the over-encapsulated formulation will be marketed but the tablets. According to the Applicant the over-encapsulated tablets have been manufactured using the final marketing iloperidone tablet formulation. These over-encapsulated tablets

are tablets that were over-encapsulated with a gelatine capsule for blinding purposes. Bioequivalence between the final marketing formulation and the formulation used in pivotal phase III studies was established by the Applicant (please see Bioequivalence Study ILO5220110).

Objectives and outcomes/endpoints

In the placebo-controlled acute treatment studies, validated assessment scales were applied and analyzed for statistical difference from placebo.

Four validated assessment scales were applied in the clinical studies:

1. *Positive and Negative Syndrome Scale (PANSS), [Study 3000, VP-VYY-683-3101, 3001, 3002 and 3003]*
   The 30-item Positive and Negative Syndrome Scale (PANSS) was developed to assess the severity of symptoms of schizophrenia. The PANSS items are divided into positive, negative, and general psychopathology factors. The PANSS total score (or rating) is the sum of all 30 PANSS items taken together, with a minimum score of 30 and a maximum score of 210. All items are rated on a scale of 1 (absent) to 7 (extremely severe).

2. *Brief Psychiatric Rating Scale (BPRS), [Study 3004, 3005]*
   The Brief Psychiatric Rating Scale (BPRS) total score is derived from the individual items of the PANSS assessment. It consists of 18 items extracted from the PANSS questionnaire: six of the seven items of the positive sub-scale items (P2-P7), two of the seven items of the negative subscale items (N1-N2), and ten of the sixteen items of the general psychopathology sub-scale items (G1-G10). The possible range for the BPRS total score is 18 to 126.

3. *Clinical Global Impression of Severity (CGI-S)*, *[Study VP-VYY-683-3101]*
   The Clinical Global Impression of Severity (CGI-S) is a 7-item scale developed to assess the overall, absolute degree of illness at any point in time. A rating of 1 is equivalent to “normal, not at all ill,” and a rating of 7 is equivalent to “among the most extremely ill patients.” This rating refers to the degree of illness at the time of the visit and during the week prior to the visit.

4. *Clinical Global Impression of Change (CGI-C), [Long-term studies 3001-3003]*

   CGI-C is a 7-item scale: 1 = very much improved; 2= much improved; 3= minimally improved; 4= no change; 5= minimally worse; 6= much worse; or 7= very much worse.

In the “placebo-controlled” short-term studies 3000, 3004, 3005 and 3101 also active comparators were included (haloperidol, risperidone resp. ziprasidone). Nevertheless, formal controls to these active comparators have not been done. Primary efficacy assessment/objective was the comparison to placebo.
In the haloperidol controlled studies 3001, 3002 and 3003 the primary objective was to assess long-term efficacy at week 52 and also for week 52 no statistical inference had been planned. Therefore the short-term phases of these studies are considered only supportive for the assessment of short-term efficacy.

Summary of main studies

The following table summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Summary table

Study Identifier	Study Objective	Study Design	Test Product and Dosing Regimen	Number of Patients	Duration of Treat-ment	Primary Parameter (Change from baseline to endpoint)	Study Locations (Countries)
Dose-Finding Studies							
ILPB202 (Phase II)	Efficacy/ safety; schizophrenia	DB, R, placebo, 2 fixed doses	iloperidone capsules (HP 873), 4 mg/d or 8 mg/d vs. placebo; Application BID	Randomised Total: 104 ILO 4: 34 ILO 8: 34 Placebo: 35	Double-Blind 42 days	PANSS-T (Positive and Negative Syndrome Scale)	U.S.A.
Pivotal Studies							
ILP3000 (Phase III)	Efficacy/ safety of ILO (3 fixed dose) and HAL vs. placebo; schizophrenia/ schizo-affective dis. with acute or subacute exacerbation	DB, R, placebo, active co., 3 fixed doses	Short-term: ILO-oet 4 mg/d 8 mg/d or 12 mg/d; Appl. BID HAL-oet 15 mg/d , Appl. BID Long-term: ILO-oet 4-16 mg/d once daily HAL-oet 5-20mg/d once daily	Randomised Total: 621 ILO 4: 121 ILO 8: 125 ILO 12: 124 HAL 15: 124 Placebo: 127 Schizophrenia 69% (428)	DB-Short-Term 6 weeks DB-Long-Term 46 weeks Open Label Extension with ILO Up to 3 years	PANSS-T (week 6)	U.S.A.
ILP3004 (Phase III)	Efficacy and safety of ILO (2 dose ranges) and RIS vs. placebo; schizophrenia/schizo-affect. disorder with an acute or subacute exacerbation	DB, R, placebo, active co., flexible dose range	Short-term: ILO-oet 4-8 mg/d or 10-16 mg/d; Appl. BID RIS capsules, 4-8 mg/d; Appl. BID Long-term: ILO-oet 4-16 mg/d once daily RIS capsules 2-8 mg/d once daily	Randomised Total: 616 Placebo: 156 ILO 4-8: 153 ILO 10-16: 154 RIS: 153 Schizophrenia 78% (499)	DB-Short-Term 6 weeks DB-Long-Term 46 weeks Open Label Extension with ILO Up to 2 years	BPRS (week 6)	U.S.A., Australia, Belgium, Canada, France, Hungary and South Africa

ILP3005 (Phase III)	Efficacy / safety of ILO and RIS vs. placebo; schizophrenia/ schizo-affect. disorder	DB, R, placebo, active co. 2 flexible dose ranges	Short-term: ILO tablets, 12-16 mg/d or 20-24mg/d; Appl. BID RIS capsules, 6-8 mg/d; Appl. BID Long-term: ILO tablets, 4-24 mg/d once daily	Randomised Total: 706 Placebo: 160 ILO 12-16: 244 ILO 20-24: 145 RIS: 157 Schizophrenia 78% (548)	DB-Short-Term 6 weeks Open Label Extension with ILO Up to 2 years	BPRS (week 6)	U.S.A, Canada, Croatia, Germany, Hungary, Israel, Poland and South Africa
VP-VYV-683-3101 (Phase III)	1) efficacy/safety 2) efficacy of ILO vs. placebo each in schizophrenic patients lacking the ciliary neurotrophic factor (CNTF) FS63Ter poly-morphism	DB, R, placebo, active co., fixed dose	Short-term: ILO-oet 24 mg/d, Appl. BID Ziprasidone-oec 160 mg/d, Appl. BID Open label: ILO-oet 12 mg/d, once daily or 24 mg/d, Appl. BID	Randomised Total: 606 ILO 24: 303 ZIP: 151 Placebo: 152 Schizophrenia 100%	DB-Short-Term 4 weeks Open Label Extension with ILO Up to 26 weeks	PANSS-T (week 4)	U.S.A. and India

Long-Term Studies 3001-3003 (had the same study design, dose and endpoint)							
ILP3001 (Phase III)	efficacy/safety of ILO vs. HAL; schizophrenia / schizo-affective disorder	DB, R, active co., flexible dose range	ILO-oet 4-16 mg/d, Appl. BID HAL-oet 5-20 mg/d , Appl. BID	Randomised Total: 600 ILO: 454 HAL: 146 Schizophrenia 92% (552)	Placebo-run in (day -2 to 0) DB-Short-Term 6 weeks (day 1 to 42) DB-Long-Term 46 weeks (day 43 to 364) Open-Label Extension with ILO Up to 2.5 years	See Meta ILP3001-3 PANSS-T (week 52)	Austria, Czech Republic, France, Germany, Hungary, Israel, Poland, and Switzerland
ILP3002 (Phase III)	efficacy / safety of ILO vs. HAL; schizophrenia / schizo-affective disorder	DB, R, active co., flexible dose range	ILO-oet 4-16 mg/d, Appl. BID HAL-oet 5-20 mg/d, Appl. BID	Randomised Total: 557 ILO: 420 HAL: 137 Schizophrenia 76% (421)	see study 3001	See Meta ILP3001-3 PANSS-T (week 52)	Egypt, Hong Kong, Indonesia, Malaysia, the Philippines Singapore, Taiwan, and Thailand
ILP3003 (Phase III)	Efficacy /safety of ILO vs. HAL; schizophrenia /schizo-affect. disorder	DB, R, active co., flexible dose range	ILO-oet 4-16 mg/d , Appl. BID HAL-oet 5-20 mg/d, Appl. BID	Randomised Total: 487 ILO: 365 HAL: 122 Schizophrenia 97% (473)	see study 3001	See Meta ILP3001-3 PANSS-T (week 52)	Argentina, Brazil, Chile, Colombia, and Mexico
Meta ILP3001-3 (Phase III)	maintenance effect of ILO vs. HAL; schizophrenia/ schizo-affective disorder over 46 weeks of treatment (Pooled analysis from studies 3001, 3002 and 3003).	DB, R, active co., flexible dose range	ILO-oet 4-16 mg/d Appl. BID HAL-oet 5-20 mg/d Appl. BID	Randomised Total: 1644 ILO: 1239 HAL: 405 Schizophrenia Patients in the Analysis Population for long-term maintenance Total: 443 ILO: 337 HAL: 106	see study 3001 DB-Long-Term 46 weeks	Time to relapse	Pooled analyses! Population see above

HAL=haloperidol; ILO=iloperidone; RIS=risperidone; ZIP=ziprasidone; ILO-oet= iloperidone over-encapsulated tablets; Ziprasidone-oec = Ziprasidone over-encapsulated capsules; DB= double-blind; R= randomised; Appl.= Application; BID= twice daily

Short-term studies

Four pivotal placebo- and /or active-controlled short-term trials have been submitted (3101, 3000, 3004, 3005). Duration of the studies resp. short-term phases of these studies were 6 or 4 weeks. Primary efficacy parameter was reduction of PANSS resp. BPRS compared to placebo.

Studies 3000 and 3004 were followed by a double-blind 46 weeks long-term phase.

Table E2: *Summary of Primary Efficacy Variables at week 6 resp. week 4 in the four Pivotal Short-Term Phase III Trials;* ***Post-Hoc Analysis; Schizophrenia Only***

	PANSS Total		**BPRS**	
	Change from Baseline at Endpoint	**P Value[a]**	**Change from Baseline at Endpoint**	**P Value[a]**
3101				
Placebo (N=140)	-7.1 [-10.0, -4.2]	NA	-4.6 [-6.4, -2.8]	NA
ILO 24 mg (N=283)	**-12.0 [-14.0, -10.0]**	**0.006**	**-7.4 [-8.6, -6.2]**	**0.013**
3004				
Placebo (N=116)	-7.5 [-11.7, -3.2]	NA	-4.9 [-7.4, -2.3]	NA
ILO 4-8 mg (N=115)	-8.7 [-12.9, -4.5]	0.660	-5.8 [-8.3, -3.3]	0.581
ILO 10-16 mg (N=121)	-10.2 [-14.5, -6.0]	0.313	*-6.5 [-9.0, -4.0]*	*0.306*
3005				
Placebo (N=113)	-6.7 [-10.5, -2.8]	NA	-4.3 [-6.6, -2.0]	NA
ILO 12-16 mg (N=178)	**-11.7 [-15.0, -8.5]**	**0.034**	***-7.4 [-9.4, -5.4]***	***0.033***
ILO 20-24 mg (N=111)	**-14.7 [-18.6, -10.8]**	**0.002**	**-8.8 [-11.2, -6.4]**	**0.005**
3000				
Placebo (N=78)	-3.5 [-8.4, 1.5]	NA	-2.8 [-5.8, 0.1]	NA
ILO 4 mg (N=83)	-9.2 [-14.2, -4.3]	0.072	-6.4 [-9.3, -3.5]	0.054
ILO 8 mg (N=78)	-4.8 [-9.8, 0.2]	0.666	-4.4 [-7.3, -1.5]	0.414
ILO 12 mg (N=82)	**-10.1 [-15.0, -5.2]**	**0.037**	**-7.1 [-10.0, -4.2]**	**0.024**
ILO 8&12 mg (N=160)	*NA*	*0.148*	NA	0.076

ILO=iloperidone, NA=not applicable
[a] P value vs placebo

Study 3101

The only definite positive study of short-term efficacy of iloperidone in schizophrenia was study 3101. This study by Vanda was conducted exclusively in schizophrenic patients. This study was double-blind, and had three treatment arms: Iloperidone, placebo and ziprasidone.

There were *two primary objectives: Firstly* to evaluate the short-term efficacy of a 24-mg/d iloperidone dose compared with placebo, administered bid to patients with schizophrenia, by change of PANSS-T from baseline to Week 4, based on MMRM analysis. A *step-down objective* was to assess the efficacy of a 24-mg/d (12 mg bid) iloperidone dose in patients with schizophrenia lacking the ciliary neurotrophic factor (CNTF) FS63Ter polymorphism compared with patients with schizophrenia lacking the CNTF FS63Ter polymorphism treated with placebo.

Results: The PANSS reduction with ILO 24 mg differed statistically significant from placebo (-12.0 vs. -7.1) at week 4; iloperidone was also statistically superior to placebo in the LOCF analysis but not the OC analysis. The effect assessed by the difference to placebo seems to be modest. Patients in this study came from USA and India. Although 64% of the patients completed this study, bias induced by missing data cannot be ruled out. Lack of therapeutic effect was the reason for withdrawal of 7% to 13% of patients in each treatment group (7% in iloperidone group and nearly identical in ziprasidone group, 8%). Withdrawal of consent ranged from 14% to 20% (20% in iloperidone group). The drop-out rate was similar across all treatment groups.

Table E3 PANSS-T Adjusted Mean Change from Baseline by Week, MMRM Analysis, Study 3101 Patients with Schizophrenia

Timepoint	**ILO 24 mg/d n=283**		**ZIP 160 mg/d n=144**		**Placebo N=140**
Baseline (SD)	92.9 (13.1)		90.9 (11.5)		90.5 (11.2)
Week 4	**-12.0[c,d]**	**p=0.006**	**-12.3[a]**	**p=0.012**	-7.1

[a] p<0.05 (2-tailed) compared with placebo based on MMRM analysis using baseline as covariate.
[b] p<0.05 (2-tailed) compared with placebo based on MMRM analysis using the randomization test method (1000 iterations). The randomization test method was only applied to the iloperidone vs. placebo comparison.
[c] p<0.01 (2-tailed) compared with placebo based on MMRM analysis using baseline as covariate.
[d] p<0.01 (2-tailed) compared with placebo based on MMRM analysis using the randomization test method (1000 iterations). Source: VP-VYV-683-3101 CSR Post-text Table 9.2.1-2a

Studies 3000. 3004 and 3005

Validity of 3000, 3004 and 3005 is clearly limited, as the primary efficacy parameter was defined for the mixed population (schizophrenia plus schizoaffective disorder). In these studies efficacy analyses for the primary endpoint in the “schizophrenia-only” population were done as post hoc analyses.

Study 3000 was negative, referred to the primary end-point, which per definition was measured in the combined ILO 8 and 12 mg dose group vs. placebo, this holds for the mixed population (primary efficacy parameter) and the schizophrenia population (post hoc analysis).

Only 37% of the patients completed week 6 and especially this study is supposed to be biased. The most common reasons for premature discontinuation were unsatisfactory therapeutic effect (35% in placebo arm, 29-30% in ILO groups and with 25% a bit lower in the HAL group) and withdrawal of consent (15% to 23% across treatment groups).

The reduction of PANSS was significant in the ILO 12 mg dose group in schizophrenia (post hoc analysis). In regard to the lower doses the results in Study 3000 are heterogeneous as the 4mg performs better than the 8mg dose and also numerically slightly better compared to the 4-8 mg dose range in study 3004.

Table E4 PANSS-T Adjusted Mean Change from Baseline by Week, LOCF Analysis, Study 3000 Patients with Schizophrenia

Timepoint	ILO 4 mg/d n=83		ILO 8 mg/d n=78		ILO 12 mg/d n=82		HAL 15 mg/d n=70		Placeb n=78
Baseline (SD)	97.0 (15.7)		96.4 (16.1)		94.4 (14.6)		98.6 (15.5)		96.3 (18.2)
week 6	-9.2	p=0.072	-4.8	p=0.666	**-10.1***	**p=0.037**	**-12.9***	**p=0.005**	

N=number of patients; ILO=iloperidone; HAL=haloperidol
*** p<0.05 (two-tailed) compared with placebo; based on t test using ANCOVA model.**

Study 3005

In study 3005 a primary treatment comparison was done in the mixed population between ILO 12-16 mg/d and placebo. If this test was significant at the 0.05 level, a subsequent comparison was done with the ILO 20-24 mg/d group and placebo. As the comparison of ILO 12-16 mg/d and placebo in regard to reduction of BPRS was not statistically significant in the mixed population, this study failed in the mixed population. Whereas in study 3005 a statistically significant reduction of BPRS compared to placebo was seen with the ILO 12-16 mg/d and ILO 20-24 mg/d dose group in schizophrenia (post hoc analyses). This might be considered supportive for an efficacious dose range of iloperidone 12-24 mg/d. Nevertheless, only 58% of the patients completed week 6 and the missing data could induce a bias to the study results. In study 3005 the iloperidone groups had a higher rate of overall discontinuation compared to the risperidone arm (46% and 41% compared to 29%). In the groups ILO-12-16 mg/d and ILO 20-24mg/d each 23% dropped out due to therapeutic unsatisfactory effect and in RIS-group only 8%.

In study 3005 also impact of CNTF FS63Ter polymorphism was analysed.

Table E5 BPRS Adjusted Mean Change from Baseline by Week, LOCF Analysis, Study 3005 Patients with Schizophrenia

Timepoint	ILO 12-16 mg/d n=178		ILO 20-24 mg/d n=111		RIS 6-8mg/d n=119		Placebo n=113
Baseline (SD)	54.6 (7.5)		55.1 (8.1)		55.6 (8.6)		55.5 (8.7)
week 6	**-7.4***	**p=0.033**	**-8.8***	**p=0.005**	**-11.4***	**p<0.001**	-4.3

N=number of patients; ILO=iloperidone; RIS=risperidone
*** p<0.05 (two-tailed) compared with placebo; based on t test using ANCOVA model.**

Study 3004

Study 3004 with ILO 4-8 mg/d and ILO 10-16 mg/d was negative for the schizophrenia population, which showed a non-significant change of BPRS compared to placebo. In the mixed population the change of BPRS in the ILO 10-16 mg/d differed statistically significant from placebo (primary efficacy parameter) and differed also statistically significant in the ILO 4-8 mg/d dose group. Nevertheless, only 51% of the patients completed week 6 and the missing data could induce a bias to the study results. Completion rate was best in the RIS group and ILO 10-16 mg/d group (58% resp. 56%) and lower with ILO 4-8 mg/d (48%) and placebo (40%). Discontinuation due to unsatisfactory therapeutic effect was more frequent in the ILO group 4-8 mg/d (24%) and ILO 10-16 mg/d (21%) compared to the RIS group (16%).

Table E6 BPRS Adjusted Mean Change from Baseline by Week, LOCF Analysis, Study 3004 Patients with Schizophrenia

Timepoint	ILO 4-8 mg/d n=115		ILO 10-16 mg/d n=121		RIS 4-8mg/d n=110		Placebo n=116
Baseline (SD)	54.9 (9.1)		53.3 (9.1)		54.3 (9.9)		53.5 (9.5)
week 6	-5.8	p=0.581	-6.5	p=0.306	**-10.3***	**p<0.001**	-4.9

N=number of patients; ILO=iloperidone; RIS=risperidone

*** p<0.05 (two-tailed) compared with placebo; based on t test using ANCOVA model.**

Secondary endpoints

In study 3101 with an exclusively schizophrenic population also the secondary variables BPRS, PANSS-P (-4.2 vs. -2.2), PANSS-N (-2.7 vs. -1.7) and CGI-S (-0.7 vs. -0.4) improved significantly at week 4 compared to placebo. Nevertheless clinical relevance of these results seemed moderate.

Comparators

All short-term placebo-controlled pivotal studies included an active comparator arm. However these studies were not powered to formally compare iloperidone and the active comparators.

In the short-term studies 3004 and 3005 risperidone 4-8 mg resp. 6-8 mg performed numerically better than ILO 4-8 mg or ILO 10-16 mg and risperidone 6-8 mg performed numerically better than ILO 10-16 mg and ILO 20-24 mg. The dose-range of risperidone applied was slightly higher than today usually recommended. Nevertheless in study 3005 the maximum dose of ILO 20-24 mg/d has been applied and the risperidone arm performed numerically better also in comparison to this dose-arm. Also it is noteworthy that the drop out due to unsatisfactory therapeutic response was considerably higher with iloperidone compared to risperidone.

In short-term study 3000 haloperidol 15 mg/d performed numerically better than iloperidone 12 mg/d and in the iloperidone arms the drop out due to unsatisfactory therapeutic effect was 4-5% higher compared to haloperidol. According to the SPC of haloperidol in acute schizophrenia the starting dose is 5-10 mg/d; a daily dose of haloperidol 30 mg/d usually should not be exceeded. Nevertheless the dose of HAL in the short-term study appears rather high compared to today usually applied doses, possibly favouring haloperidol.

Ziprasidone performed similarly to iloperidone in short-term study 3101. The maximum recommended dose for ILO (24mg/d) was compared to the maximum recommended dose of ziprasidone (160 mg/d) (please see e.g. SPC of Zeldox). Both doses applied refer to the treatment of acute schizophrenia and doses are considered adequate. Drop out due to lack of therapeutic effect was comparable between iloperidone and ziprasidone.

For better estimation of the clinical relevance of the results for the short-term trials in the schizophrenia population percentage of CGI-C “very much” or “much improved” (resp. if not available the analysis by CGI-S) and additionally a responder analyses have been provided at day 150 (post hoc) with the percentage of patients who had at least a 30% and 40% reduction on the total PANSS compared to baseline. The results are not convincing since only 30% response results are significantly different from placebo for one (Study 3005) of the two the most relevant Studies 3005 and 3101.

In regard to CGI-C only in short-term study 3101 but not in study 3005 a response statistically significant different from placebo was observed with iloperidone; nevertheless the difference to placebo was small (29.3% with ILO compared to 21.4% with placebo). From a clinical point of view this is a modest result.

Responder Analyses

Responder analyses were performed post-hoc to better inform the clinical relevance of the results

- PANSSt/BPRS % reduction (discontinuing patients counted as non-responders)

Table E7: Study 3000, 30% Responder Analysis, PANSS-T, Schizophrenia Patients

Timepoint	ILO 4 mg/d n=83		ILO 8 mg/d n=78		ILO 12 mg/d n=82		HAL 15 mg/d n=70		Placebo n=78
30% Response week 6	13.3%	p=0.293	6.4%	p=0.807	9.8%	p=0.754	17.1%	p=0.134	7.7%

N=number of patients; ILO=iloperidone; HAL=haloperidol

Table E8: Study 3004, 30% Responder Analysis, BPRS, Schizophrenia Patients

Timepoint	ILO 4-8 mg/d n=115		ILO 10-16 mg/d n=121		RIS 4-8 mg/d n=110		Placebo n=116
30% Response week 6	16.5%	p=0.357	20.7%	p=0.180	24.5%	p=0.035	12.9%

Table E9: Study 3005, 30% Responder Analysis, BPRS, Schizophrenia Patients

Timepoint	ILO 12-16 mg/d n=178		ILO 20-24 mg/d n=111		RIS 6-8 mg/d n=119		Placebo n=113
30% Response week 6	25.3%	p=0.040	22.5%	p=0.052	34.5%	p=0.002	13.3%

N=number of patients; ILO=iloperidone; RIS=risperidone

Table E9: Study 3005, 30% Responder Analysis, BPRS, Schizophrenia Patients, ≥2Weeks of Treatment

Timepoint	ILO 12-16 mg/d n=134		ILO 20-24 mg/d n=90		RIS 6-8 mg/d n=107		Placebo n=89
30% Response week 6	33.6%	p=0.023	27.8%	p=0.030	38.3%	p=0.005	16.9%

N=number of patients; ILO=iloperidone; RIS=risperidone

Table E10: Study 3101, 30% Responder Analysis, PANSS-T

Timepoint	ILO 24 mg/d n=283		ZIP 160 mg/d n=144		Placebo n=140
30% Response week 4	15.9%	p=0.404	18.1%	p=0.158	12.1%

A significant different 30% response rate compared to placebo was reached with iloperidone only in study 3005: 30% responder rates were achieved in study 3005 at week 6 for iloperidone 12-16 mg/d

and 20-24 mg/d, respectively compared to earlier and more robust responder rates for risperidone 6-8 mg/d from week 3-6. (25.3%, 22.5% 34.5% resp. 13.3%; ILO 12-16, ILO 20-24, risperidone resp. placebo). In two of the short-term studies also the comparators haloperidol and ziprasidone did not reach a 30% response rate significantly different from placebo. On the other hand also in short-term study 3004 with risperidone the 30% response rate differed statistically significant from placebo.

- CGI-C (discontinuing patients counted as non-responders)

Responder is defined as a CGI-C score less than 3, which means "very much" or "much improved".

Table E11: Study 3000, Responder Analysis, CGI-C, Schizophrenia Patients

Timepoint	ILO 4 mg/d n=83		ILO 8 mg/d n=78		ILO 12 mg/d n=82		HAL 15 mg/d n=70		Placebo n=78
Week 6	18.1%	p=0.432	16.7%	p=0.499	20.7%	p=0.168	25.7%	p=0.018	14.1%

N=number of patients; ILO=iloperidone; HAL=haloperidol

Table E12: Study 3004, Responder Analysis, CGI-C, Schizophrenia Patients

Timepoint	ILO 4-8 mg/d n=115		ILO 10-16 mg/d n=121		RIS 4-8 mg/d n=110		Placebo n=116
Week 6	18.3%	p=0.743	28.1%	p=0.100	33.6%	p=0.008	18.1%

N=number of patients; ILO=iloperidone; RIS=risperidone

Table E13: Study 3005, Responder Analysis, CGI-C, Schizophrenia Patients

Timepoint	ILO 12-16 mg/d n=178		ILO 20-24 mg/d n=111		RIS 6-8 mg/d n=119		Placebo n=113
Week 6	30.3%	p=0.569	29.7%	p=0.328	47.1%	p<0.001	23.9%

N=number of patients; ILO=iloperidone; RIS=risperidone

Table E14: Study 3005, Responder Analysis, CGI-C, Schizophrenia Patients, ≥2Weeks of Treatment

Timepoint	ILO 12-16 mg/d n=134		ILO 20-24 mg/d n=90		RIS 6-8 mg/d n=107		Placebo n=89
Week 6	40.3%	p=0.387	36.7%	p=0.159	52.3%	p=0.004	30.3%

N=number of patients; ILO=iloperidone; RIS=risperidone

Table E15: Study 3101, Responder Analysis, CGI-C

Timepoint	ILO 24 mg/d n=283		ZIP 160 mg/d n=144		Placebo n=140
Week 4	29.3%	p=0.037	27.1%	p=0.254	21.4%

N=number of patients; ILO=iloperidone; ZIP=ziprasidone

The Tables E11-E15 above show the Responder Analyses based on Clinical Global Impression of Change (CGI-C) and present the percentage of patients who improved very much or much.

Only in short-term study 3101 a response statistically significant different from placebo and based on CGI-C was observed with iloperidone; nevertheless the difference to placebo was small (29.3% with ILO compared to 21.4% with placebo). From a clinical point of view this is a modest result.

In the different studies, risperidone and haloperidol reached a response (CGI-C) statistically significant different from placebo, whereas ziprasidone did not. CGI-C based responder analyses can be easily interpreted and significant results compared to placebo support conclusions on efficacy of the active treatment.

Gender and dosage (mg/kg)

Efficacy analyses in regard to sex and dose/kg have been presented. In study 3005 a significant reduction of BPRS with iloperidone 12-16 and 20-24 mg/d was only seen in females. In study 3101 a significant reduction of PANSS was seen both in females and males with ILO 24 mg/d. In an additional analysis of study 3005 only referring to patients who completed two weeks of treatment a significant reduction of BPRS was observed both in females and males with ILO 12-16, ILO 20-24 mg/d.

In the short-term studies 3005 and 3101 higher doses based on mg/kg performed better than lower doses. In study 3005 with iloperidone 0.2 - 0.3 and ≥ 0.3 mg/d and in study 3101 with 0.3 - 0.4 and ≥ 0.4 mg/d a significant reduction of the schizophrenia symptom score was observed. In both studies the effect of symptom score reduction was more pronounced with increasing dose/kg. Again the additional analysis 3005, referring only to patients who completed at least 2 weeks in the study, did not show a special trend. In this patient group a similar and significant effect was seen based on different dose/kg categories.

In the meta-analysis of long-term studies 3001-3003 a trend for dose/kg-dependent effect could not be confirmed. Nevertheless in the long-term studies relative low doses of 4 to maximal 16 mg iloperidone per day were applied to the patients.

Concomitant benzodiazepine use

Concomitant use of benzodiazepine during the studies was very frequent. Available data from the short and long term studies show that a concomitant use of benzodiazepines and ILO was similarly or less frequent than compared to concomitant use of benzodiazepines and active comparators. Discontinuation rates due to significant dose increase of benzodiazepine therapy or rates of patients who stayed on the same benzodiazepine dose are lacking.

Concomitant anticholinergics use

In the pivotal short-term trials (studies 3000, 3004, 3005 and 3101) anticholinergics were only used in 0%-1% of the treatment groups. There were no remarkable differences of anticholinergic use in the test product groups, placebo group and active control group. In the long-term trials 3001-3003 anticholinergics have not been used at all. An effect on efficacy based on use of anticholinergic substances is considered unlikely.

EU-representation in short-term clinical trials

The Applicant has presented an important analysis on the EU-population of the long-term study 3001 (80% schizophrenic EU-population). The other two long-term studies 3002 and 3003 do not include EU-sites. In the short –term studies 3004 and 3005 only 20-25% of patients are included from EU-sites; the other short-term studies do not include EU –sites at all.

The subgroup analysis of study 3001 showed that the EU-population in this study has a good and clinically relevant short-term as well long-term effect comparable to haloperidol (55% of the patients

with ILO and 58% of those with HAL had a ≥30% improvement in PANSS-T) and the effect was consistent over time and moreover consistent with the overall analysis, however these were not pre-defined analyses.

Importantly, in short-term study 3005, EU-population, only the 20-24 mg/d dose group showed a significant reduction of BPRS compared to placebo, the 12-16 mg/d dose group did not differ statistically significant from placebo. Whereas in the overall population both dose groups differed statistically significant from placebo. Therefore the appropriateness of the 12-16 mg/d dose for the EU-population might be questioned.

Sensitivity analyses

Sensitivity analyses with regard to short-term efficacy have been presented and are acceptable. The MI analysis provided by the applicant is considered the most relevant sensitivity analysis. The imputation of data from the placebo group is sufficiently conservative and the multiple imputation approach avoids an underestimation of the variance. Although the conservative nature of the approach has to be taken into account, results are not completely convincing, as in Study 3005 only the higher iloperidone dose group 20-24 mg/d and risperidone show significant differences compared to placebo. In study 3101 the iloperidone 24 mg/ d and ziprasidone group show significant differences compared to placebo. As expected, treatment effect estimates are smaller than with the MMRM approach but not by a large margin.

For study 3005 an additional MI analysis was presented based only on patients who had at least completed 2 weeks of treatment. This analysis was more favorable, a statistical significant difference from placebo was observed for both ILO 12-16 und ILO 20-24 mg/d. The intention for this adjustment of data was to account for titration differences between iloperidone and risperidone to allow a more proper comparative analysis of these two agents within the study. The rational for this need of adjustment was thus differences in time to reach target dose/steady-state conditions. For risperidone, a target dose was reached at Day 2.
For iloperidone, target dose was achieved in a week and steady-state is expected to be reached in 7-10 days. About 75% of the patients included in Study 3005 remained in the study for at least 2 weeks and were expected to have achieved steady-state conditions during that time period. For this subpopulation of patients with schizophrenia remaining in the study, significant and similar treatment effects were shown for both ILO 12-16 und ILO 20-24 mg/d and for risperidone beginning from week 3 having only a slight numerical advantage in regard to the treatment effect. On the other hand, the results of this subpopulation is limited by the fact that 25% of the patients discontinuing from the study could be expected to have dropped out due to intolerance, treatment emergent adverse events, lack of efficacy and secondary compliance difficulties. This selection of a subpopulation that did not discontinue treatment adds a bias and inflicts ambiguity to the interpretation of the results.

Long-term efficacy

Long-term efficacy has been evaluated in three double-blind, randomized, haloperidol-controlled studies in a total of 1446 schizophrenic patients (studies 3001, 3002, 3003). These studies had identical study design, an identical flexible dose range and duration in each was 52 weeks. In each of these studies ILO 4-16 mg/d was applied and HAL 5-20 mg/d. Also in the long-term studies, a mixture of schizophrenic and schizoaffective patients has been included. Nevertheless most of the patients had schizophrenia (92%, 76% resp. 97%). The dose range of haloperidol in the long-term studies appears rather high compared to today usually applied doses for maintenance therapy.

The objectives of the studies were the following:

1) To compare maintenance effect of ILO 4-16 mg/d to HAL in patients with schizophrenia or schizoaffective disorder over 46 weeks of treatment by time to relapse (pooled analysis from studies 3001-3003).

   Definitions:

   Response: PANSS ⩽ 60 (i.e. ~ mildly ill) or CGI at least minimally improved at week 6

   Relapse: -Worsening of PANSS ⩾ 20% compared to week 6 or

   -Drop out due to unsatisfactory therapeutic effect

   Analysis Population:

   Patients who responded to treatment during the initial double-blind phase were included in the analysis population.

2) To compare the long-term efficacy of ILO 4-16 mg/d to HAL at week 52 by change of PANSS in patients with schizophrenia or schizoaffective disorder at study level (no inferential statistics).

Ad 1) Pooled analysis for time to relapse, pre-defined analysis

Methods: Time to first relapse from a proportional hazards model for patients responding to treatment after 6 weeks was implemented as primary variable for the pooled analysis and a non-inferiority margin was defined for the comparison of iloperidone to haloperidol. The non-inferiority margin was translated from a fixed margin of 15 percentage points (assuming 30% relapsers in the haloperidol group) to an upper bound of the relapse hazard ratio of 1.676. This non-inferiority margin is considered to wide. Moreover from a clinical point of view the original definition of “response” at week 6 is not considered appropriate.

Results:

The results of the predefined primary analysis was based on selected subgroups of responders at day 42 and these indicate that iloperidone is not non-inferior to haloperidol with a relapse hazard ratio of 1.340 and a 95%-CI of (1.001, 1.795). The upper bound of the 95%-CI is above the predefined NI margin of 1.676. Moreover the non-inferiority margin in this predefined primary analysis was quite wide, as the upper bound of the relapse hazard ratio of 1.676 translates to a margin of 15 percentage points in treatment effect difference. Most important from a clinical point of view, the response definition chosen for the predefined analysis was not appropriate.

Conclusion: Long-term efficacy has not been demonstrated in the predefined pooled analysis and ILO 4-16 mg/d was not non-inferior to haloperidol in regard to time to relapse.

Table - Pre-defined long-term efficacy analysis: Pooled analysis of long-term studies 3001-3003:

Covariate	Regression Coefficient	Standard Error	P-value+	Hazard ratio	95% CI of Hazard ratio++
Baseline PANSS total	-0.005691	0.00310	0.0666	NA	NA
Treatment (Ilo vs Hal)	0.292926	0.14904	0.0494	1.340	1.001, 1.795

+ P values based on Wald tests from the proportional hazard model.
The hazard model includes baseline PANSS total score and treament as covariate.
++ Ilo is considered non-inferior to Hal if upper bound is not greater than 1.676.
NA = Not Applicable

13:30/10APR2001/Page: 1 of 1

Program Name: studya1:[study.novartis.ilpcom123.analysis]pkap6.sas
Iloperidone Study No.: Pooled analysis of 3001, 3002, and 3003

Ad 2) Mean change of PANSS at week 52, long-term studies-table E16

Iloperidone			Haloperidol		
3001 (n=443)	**3002** (n=412)	**3003** (n=360)	**3001** (n=145)	**3002** (n=136)	**3003** (n=122)
Baseline (SD)					
89.4 (17.1)	90.3 (20.4)	93.2 (21.7)	89.4 (16.1)	92.5 (22.0)	92.6 (18.9)
Mean Change from Baseline at Week 1					
-3.7	-6.4	-4.8	-3.9	-7.0	-5.7
Mean Change from Baseline at Week 6					
-11.9	-21.6	-14.2	-12.3	-23.3	-14.9
Mean Change from Baseline at Week 26					
-8.4	-23.3	-16.4	-8.1	-25.3	-17.6
Mean Change from Baseline at Week 52					
-7.1	**-24.1**	**-17.4**	**-8.4**	**-24.5**	**-19.4**

LOCF=last observation carried forward
Source: ILP3001 CSR Table 9-1, ILP3001 Post-text Table 9.2.6-1, ILP3002 CSR Table 9-1, ILP3002 Post-text Table 9.2.6-1, ILP3003 CSR Table 9-1, ILP3003 Post-text Table 9.2.6-1

Mean PANSS-T values decreased consistently from Week 1 through Week 6 and up through Week 52 in the long-term studies apart from study 3001. All studies had a considerable drop-out. Only 31% of the patients in study 3001, 51% in study 3002 and 57 % in study 3003 in the iloperidone treatment arms completed the 52 weeks protocol. Completion rates in the haloperidol arms were similar. Nevertheless in the ILO group an unsatisfactory therapeutic effect was a slightly more frequent reason for drop out than compared to the HAL group in studies 3001 and 3003 (31% vs. 25% and 19% vs. 11%). In study 3002 the drop out rate due to unsatisfactory therapeutic effect was identical in the ILO and HAL group.

Numerical comparisons of change from baseline in the PANSS total score between active comparator and iloperidone in the 3001, 3002, and 3003 studies are presented using the LOCF and OC (patients who completed the treatment phase) data. These comparisons could be biased by the high drop-out rates for the LOCF imputed dataset as well as for the OC dataset; and especially study 3001 is supposed to be biased, as only 31% of the patients completed 52 weeks. Although the numbers suggest only a small numerical difference in favour of the active comparator, considerable bias due to missing data cannot be ruled out. Results of these separate analyses per study are considered supportive only and no inferential statistics were to be presented according to the analysis plans.

Effect of the treatment on cognitive function has not been evaluated.

Post-hoc analysis of long-term efficacy using a new definition of response

Post-hoc analyses on selected subgroups of responders with a CHMP-recommended and clinically appropriate definition of a responder (>30% change in PANSS) show that iloperidone would be non-inferior to haloperidol with an upper bound of the CI smaller than the pre-defined threshold (1.363 vs. 1.676). This suggests that if the absolute non-inferiority margin was 8%, iloperidone would have been shown to be non-inferior to haloperidol. Sensitivity analyses with different responder criteria in the range of 30% change in PANSS suggest that if an absolute non-inferiority margin would be set to 11%, non-inferiority could be concluded. Possible choice of non-inferiority margins is discussed by the applicant in the context of results of other antipsychotic substances. Moreover an analysis based on the Zypadhera EPAR relapse and response criteria supports non-inferiority of iloperidone.

Although the presented analyses support non-inferiority conclusions for a range of non-inferiority margins as adequately discussed by the applicant, there remain major deficiencies of the analyses: The analyses are not based on randomised groups and all additional analyses performed are post-hoc analyses. Drop out in the initial DB phase until day 42 was 19% (iloperidone) vs. 26% (haloperidol). Although drop out due to unsatisfactory therapeutic effect was similar 8% (iloperidone) and 7% (haloperidol) still bias due to selection cannot be excluded as there was no randomization prior to entry in the subsequent DB phase which lasted until week 52. For the presented post-hoc analyses type I error is not controlled, as would be normally acceptable for demonstration of long-tern efficacy. Therefore it is concluded that for iloperidone long-term efficacy has not been sufficiently demonstrated.

Proposed dose for long-term treatment

The Applicant proposed a revised dose range of 12-16 mg for long-term treatment instead of previously 12mg/d. The dose range used in the long-term studies was 4-16 mg/d. The Applicant argued that the most commonly used dose was 12 mg/d and that 64% of patients took 16mg/d at one point during the long-term phase of the studies.

Analysis performed across trials (pooled analyses and meta-analysis)

Methodology of efficacy analysis on special populations, short-term studies - age, gender, ethnicity, diagnosis and anticholinergic use:

SCE Pooled Population Dose Groups, short-term studies

All doses in the pivotal efficacy studies were given using a BID (twice daily) regimen per a fixed titration schedule to achieve the targeted maintenance dose or dose range. For the pooled analysis, patients were allocated to one of three dose groups of iloperidone (Table E19). Assignment to a dose group was based on randomization, rather than on the exact dose levels to which patients were exposed.

Three active controls (haloperidol 15 mg/day, risperidone 4-8 mg/day, and ziprasidone 160 mg/day) are presented in the results for reference purposes. While no formal comparisons to iloperidone were made, the comparable performance of iloperidone to these active controls was discussed.

Table E19: Treatment Groups for Pooled Analysis *(short-term studies)*

Study Number	PBO	ILO 4-8 mg/day	ILO 10-16 mg/day	ILO 20-24 mg/day	HAL 15 mg/day	RIS 4-8 mg/day	ZIP 160 mg/day
3000	PBO	4 mg, 8 mg	12 mg		15 mg		
3004	PBO	4-8 mg	10-16 mg			4-8 mg	
3005	PBO		12-16 mg	20-24 mg		6-8 mg	
3101	PBO			24 mg			160 mg

HAL=haloperidol; ILO=iloperidone; PBO=placebo; RIS=risperidone; ZIP=ziprasidone

SCE Pooled Population Subgroups

Demographic subgroups of patients examined in the pooled SCE analyses are:

- age (<50 years, ≥50 years);
- sex (male, female);
- race (Asian, Black or African American, White, or Other);
- diagnosis, as defined by Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) classification of schizophrenia [disorganized (295.10), catatonic (295.20), paranoid (295.30), residual (295.60), undifferentiated (295.90)] and schizoaffective disorder (295.70); and
- Concomitant anticholinergic use (present, absent).

PANSS-T, BPRS and CGI-S scores were analyzed by population subgroups.

Subgroup analyses were done for pooled studies (3000, 3004, 3005, 3101). The informative value of these analyses is limited as the studies have been pooled and dose ranges have been established which might lead to bias. According to the Applicant age, gender or race did not have any effect on responsiveness.

Additional subgroup analyses for the four short-term trials and the pooled long-term studies according to age, sex, dose/kg, and BMI in regard to the primary efficacy parameter have been provided by the applicant. Due to the small numbers of patients in some subgroups significance cannot be reached and no clear trend is perceivable.

In regard to efficacy by dose/kg: For studies 3000, 3004 and 3001 in addition an efficacy analysis should be submitted for patients receiving 0.2-0.3 mg/kg iloperidone (provided there are enough patients in this dose range) to be comparable with the dose ranges used in studies 3005 and 3101.

Clinical studies in special populations

1) *Efficacy Based on Ciliary Neurotrophic Factor (CNTF) Genotype*

Study 3101

The step-down objective of the study was to assess the efficacy of a 24-mg/d (12 mg BID) iloperidone dose in patients with schizophrenia lacking the ciliary neurotrophic factor (CNTF) FS63Ter

polymorphism compared with patients with schizophrenia lacking the CNTF FS63Ter polymorphism treated with placebo. This analysis demonstrated that patients who are CNTF FS63Ter(-) when treated with iloperidone appear to have a greater placebo subtracted improvement from baseline compared to patients who are CNTF FS63Ter(+). Similar results were observed for the other efficacy scales. Comparison to the improvement in the overall population indicated that CNTF FS63Ter(-) patients experienced greater improvement versus placebo as compared to all patients treated with iloperidone.

The results indicated that wild type gene expression of CNTF may be a marker for response to iloperidone in the treatment of schizophrenia.

Impact of CNTF FS63Ter poly-morphism was also evaluated in pivotal study 3005 and similar results were obtained:

Study 3005

Patients enrolled in study 3005 were given the option of participating in a pharmacogenetics sub-study, the goal of which was to identify genetic markers that associate with iloperidone efficacy. 39% (207/532) consented to participate in the sub-study. In assessing the association of efficacy with the CNTF FS63Ter polymorphism, iloperidone efficacy was calculated using the same statistical model used to evaluate the primary efficacy variable for the overall ILP3005 trial.

Associations between genotypes and iloperidone effectiveness were determined using an ANCOVA model. FS63Ter(+) patients (heterozygotes and homozygotes) were included in one group, FS63Ter(-) patients, that is, those with two wildtype copies of CNTF, were included in the other. To correct for the testing of SNPs in multiple genes, all p-values were subjected to corrections using the Bonferroni method and were also studied with bootstrap approaches in order to obtain better estimates of significance. The results also from Study 3005 suggest greater improvement in the wild-type carriers of the CNTF gene [FS63Ter(-)] over baseline in PANSS-T-scores at Week 6 than for patients who harbour the CNTF polymorphism (please see Table below).

Table E17: PANSS-T LS Mean change from baseline at Week 6: Analysis of covariance for LOCF dataset comparing CNTF FS63Ter (-) vs. FS63Ter (+), Study 3005

	CNTF-FS63Ter (-) (95% CI)	*CNTF-FS63Ter(+)* (95% CI)	*FS63Ter(-) vs. (+)* comparison
ILO 12-16 mg	-21.38 (-26.4, -16.3) N=56	-6.90 (-14.8, 0.9) N=20	p=0.0032 [A]
ILO 20-24 mg	-15.64 (-22.0, -9.3) N=34	-3.11 (-21.4, 15.2) N=5	p=0.0902
All ILO	-20.16 (-24.4, -15.8) N=90	-8.06 (-15.1, -1.0) N=25	p=0.0017 [B]
RIS 6-8 mg	-19.34 (-24.8, -13.9) N=42	-16.74 (-28.0, -5.5) N=11	p=0.5418
Placebo	-12.83 (-19.4, -6.3) N=34	0.99 (-14.0, 16.0) N=10	p=0.0875

[A]p<0.023 after Bonferroni correction; [B]p<0.0126 after Bonferroni correction

In contrast to the highly significant differences between response of FS63Ter(+) and (-) patients to iloperidone, FS63Ter status was not associated with response among placebo patients, or those randomized to the risperidone arm of the study. This finding suggests that while CNTF FS63Ter predicts response to iloperidone, it may not predict response to other treatments.

2) *Efficacy analysis on special populations - age, gender, ethnicity, diagnosis and anticholinergic use*

Subgroup analyses for the short-term studies were done by pooled analysis. The informative value of these analyses is limited as the studies have been pooled and dose ranges have been established which might lead to bias. For methodology of this pooled analysis please see the following section below ("*Analysis performed across trials*"). In the analysis by age, patients were divided into those younger than 50 years and those older than 50 years. Regarding the inclusion criterion "age" patients from 17 to 69 years of age could be included into the clinical studies. Therefore data for elderly are limited, data for children are absent and data for adolescents are also limited. Analyses were also performed by sex, ethnicity (White, Black, Asian, "Other"), and concomitant diagnosis as defined by Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) classification of schizophrenia and schizoaffective disorder, respectively, and anticholinergic use (yes/no).

Efficacy analysis by age: No clear trend was perceivable.

Efficacy analysis by sex: In study 3005 a significant reduction of BPRS with iloperidone 12-16 and 20-24 mg/d was only seen in females. In study 3101 a significant reduction of PANSS was seen both in females and males with ILO 24 mg/d. Table 58 presents an additional analysis of study 3005, referring only to patients who completed at least 2 weeks in the study. Based on this analysis a significant reduction of BPRS was observed both in females and males with ILO 12-16, ILO 20-24 mg/d and risperidone. Nevertheless it might be assumed from the other tables that females have an effect with 12-24 mg/d whereas males need higher doses and have an effect only with 24 mg/d. Based on the population PK, no firm conclusion can be drawn with respect to gender. The Applicant is aked to update section 5.2 of the SPC in regard to larger exposure for each of iloperidone, P88 and P95 in women compared to men having adjusted for body weight. Also the information in regard to higher dose needed in men compared to women and more pronounced effect of symptom score reduction in study 3005 and 3101 in the total population with increasing dose/kg should be reflected (see beleow).

Efficacy analsis by dose/kg**:** In study 3000 and 3004 relatively low doses of iloperidone have been used, up to 8 rep. 16 mg/d. In comparison to study 3101 and 3005 dose categories with lower limits have been set up, so these categories are not strictly comparable. In study 3000 and 3004 in none of the dose categories, also not with the "highest" doses per kg ≥ 0.1 resp. 0.2 mg/kg a significant reduction of schizophrenia symptom score was observed.

Whereas in study 3005 with iloperidone 0.2 - 0.3 and ≥ 0.3 mg/d and in study 3101 with 0.3 - 0.4 and ≥ 0.4 mg/d of the schizophrenia symptom score was observed, in both studies the effect of symptom score reduction was more pronounced with increasing dose/kg.

Efficacy analysis by BMI: The effects in the different BMI-categories are heterogeneous and no clear trend is perceivable in regard to a BMI-related efficacy analysis.

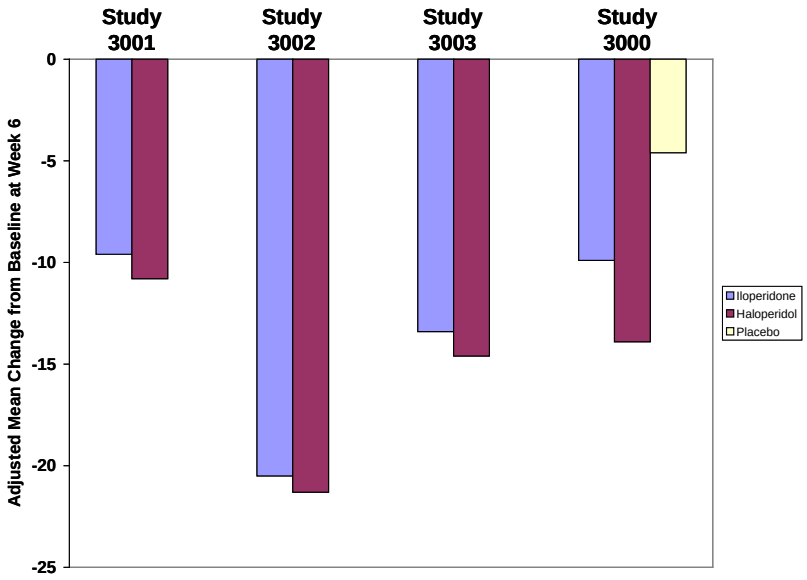
Supportive study(ies)

1) Active-controlled short-term phases of studies 3001-3003

Results for the acute treatment phases of the haloperidol-controlled long-term studies Studies 3001, 3002 and 3003 support the effectiveness of iloperidone for short-term treatment of schizophrenia by reduction of PANSS at week 6. They are considered supportive only, as the primary objective was to

compare the long-term efficacy of ILO 4-16 mg/d to HAL 5.20 mg/d at week 52 by change of PANSS in patients with schizophrenia or schizoaffective disorder, and also for week 52 inferential statistics had not been planned. The majority of the patients in these studies had diagnoses of schizophrenia. Evaluation of change in PANSS-T scale score from baseline to Week 6 in each study showed that for each, there was a numerically comparable effect of iloperidone and haloperidol.

Figure 2: PANSS Total Score Mean Change from Baseline at Week 6, LOCF Analysis of Studies 3001, 3002, and 3003 Compared to the Placebo-Controlled Study 3000



Note: For Study 3001, only the iloperidone 12 mg/day data is shown. None of the differences between iloperidone and haloperidol are significant in Studies 3001, 3002 or 3003.

2) Long-term phases of studies 3000 and 3004

The results of the double-blind long-term phases of study 3000 and study 3004 have not been reported by the Applicant. As only 26 resp. 53 patients have completed the long-term phase, the results are not considered valid.

2.5.2. Discussion on clinical efficacy

All but one of the pivotal studies included a mixture of patients with *either* schizoaffective disorder *or* schizophrenia diagnosis as defined by Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) classification.

Short-term Studies *(3101, 3000, 3004 and 3005)*

The only definite positive study of short-term efficacy of iloperidone in schizophrenia was study 3101. This study was conducted exclusively in schizophrenic patients. This study was double-blind, and had three treatment arms: Iloperidone 24mg/d, placebo and ziprasidone 160mg/d.

Results: The PANSS reduction with ILO 24 mg differed statistically significant from placebo (-12.0 vs. -7.1) at week 4. The effect assessed by the difference to placebo seems to be modest. Patients in this study came from USA and India. Although 64% of the patients completed this study, bias induced by missing data cannot be ruled out.

Taken together the remaining three studies are considered supportive for short-term efficacy of iloperidone 12-16 mg d and 24 mg/d in schizophrenia. Nevertheless in detail these studies also show that the ILO 10-16 mg/d dose group did not separate statistically significant from placebo in one study (study 3004). In regard to the lower doses the results in Study 3000 are heterogeneous as the 4mg performs better than the 8mg dose and also numerically slightly better compared to the 4-8 mg dose range in study 3004. Nevertheless study 3000 will have to be disregarded due to an extremely high discontinuation rate at week 6 (63% of the patients discontinued).

The efficacious dose range of 12-24 mg/d is also supported by phase II dose-finding study ILPB202, testing ILO 4 or 8 mg/d capsules vs. placebo. Due to slow enrollment, this study was discontinued after 104 patients had been randomized and therefore did not reach its targeted enrollment of 120 patients. 55% of the patients completed the study. The Primary endpoint, mean change from baseline at Week 6 in PANSS, was not statistically significant from placebo. Despite the lack of statistical significance, in all parameters the ILO 8 mg/d group showed a greater numerical improvement than the ILO 4 mg/d group.

Response rates

Responder-analyses have been presented which do not deliver very strong results for iloperidone. A significant different resp. Only in study 3005, a nearly statistically significant improvement compared to placebo was reached, using 30% response rate at week 6 with iloperidone: 25.3% resp. 22.5% of the patients with ILO 12-16 resp. ILO 20-24 mg/d had a 30% response compared to 13.3% of the patients in the placebo group. Nevertheless the response rate was clinically modest. The response rate for risperidone 6-8 mg/d in this study was more robust and started from week 3-6.

In two of the other short-term studies also the comparators haloperidol and ziprasidone did not reach a 30% response rate significantly different from placebo. On the other hand in the fourth short-term study the risperidone group had a 30% response rate significantly different from placebo.

Only in short-term study 3101 a response statistically significant different from placebo and based on CGI-C was observed with iloperidone. With ILO 24 mg/d 29.3% of the patients improved “very much” or “much” compared to 27.1% with ziprasidone and 21.4% with placebo, which is a modest result.

In studies 3005 and 3101 response based on 30% reduction of PANSS and response based on CGI-C obviously was not correlated.

Blinding

The pivotal short-term placebo-controlled trials were all double-blind in study design. The Applicant comments on a possible unblinding effect of differences in side-effect occurrence between iloperidone and active comparators on efficacy and safety, with possible bias of validity especially at the early phase of the study. Such an impact on the validity of a double-blind study may certainly occur and be expected due to differences in binding profiles and psychodynamic effects of medical products that are compared by effect and safety. Iloperidone needs a longer titration period at subclinical doses compared with the active comparators included in this application due to such binding profile related tachycardia and orthostatic reactions. In Study 3101 ziprasidone was chosen. The Applicant’s choice of ziprasidone with a similar binding profile as iloperidone is acknowledged.

High Discontinuation Rates

The discontinuation rates were high in all pivotal studies for iloperidone as well as for active comparators, limiting the validity and conclusions to be drawn on efficacy for iloperidone. Nevertheless it is acknowledged that comparable drop out rates were found in other clinical trials with antipsychotics applied in schizophrenia, apart from study 3000 which had an extremely high drop out, but this might be caused by iloperidone doses too low in this study.

Sensitivity analyses

Sensitivity analyses with regard to short-term efficacy have been adequately presented. The MI analysis provided by the applicant is considered the most relevant sensitivity analysis. The imputation of data from the placebo group is sufficiently conservative and the multiple imputation approach avoids an underestimation of the variance. Although the conservative nature of the approach has to be taken into account, results are not completely convincing, as in Study 3005 only the higher iloperidone dose group 20-24 mg/d and risperidone show significant differences compared to placebo. In study 3101 the iloperidone 24 mg/ d and ziprasidone group show significant differences compared to placebo. On the other hand the haloperidol arm in study 3000 did not remain significant in the MI analysis. As expected, treatment effect estimates are smaller than with the MMRM approach but not by a large margin.

Special Populations

A step-down primary objective in two of the pivotal short-term studies (3005 and 3101) was to identify genetic markers that associate with iloperidone efficacy and furthermore determine the efficacy of iloperidone 24 mg/d compared to placebo in patients with the CNTF FS63Ter(-) genotype. Overall, patients that carry the wild-type form the CNTF gene (FS63Ter(-)) showed much greater improvement over baseline in PANSS-T scores at Week 6 than patients who harbour the CNTF polymorphism.

Children/Adolescents

A waiver for all subsets of the paediatric population for iloperidone in the treatment of schizophrenia has been granted by PDCO.

Long-term Maintenance Studies *(3001, 3002 and 3003)*

Long-term efficacy has not been demonstrated in the pre-defined analysis. In the predefined pooled analysis ILO 4-16 mg/d was not non-inferior to haloperidol in regard to time to relapse with a relapse hazard ratio of 1.340 and a 95%-CI of (1.001, 1.795). The upper bound of the 95%-CI is above the predefined NI margin of 1.676. The definition of response was not clinically appropriate and drop out in the long-term studies was high. The discontinuation rate was highest in the 3001 study where 69% of the patients compared to 49% and 43% in the 3002 and 3003 had dropped out until week 52 introducing bias to the data. Further methodological deficiencies refer to the inappropriate wide non-inferiority margin which corresponds to a 15% difference between iloperidone and haloperidol and a differential selection during the acute period with no randomisation at start of the relapse prevention period).

Separately for the long-term studies numerical comparisons of change from baseline in the PANSS total score between active comparator haloperidol and iloperidone have been presented (no inferential statistics). Mean PANSS-T values decreased consistently from Week 1 through Week 6 and up through Week 52 in the long-term studies apart from study 3001 (especially this study will be biased as only 31% of the patients completed 52 weeks). Compared to this the other two studies had less drop-out (51% resp. 57%). Although the effect of iloperdione appeared comparable to haloperidol, considerable bias cannot be ruled out for the LOCF imputed dataset as well as for the OC dataset and no sensitivity analyses are presented. Results of these separate analyses per study are considered supportive only as no inferential statistics were to be presented.

Post-hoc analysis of long-term efficacy by a new definition of response

Post-hoc analyses on selected subgroups of responders with a CHMP-recommended and clinically appropriate definition of a responder (>30% change in PANSS) show that iloperidone would be non-

inferior to haloperidol with an upper bound of the CI smaller than the pre-defined threshold (1.363 vs. 1.676). This suggests that if the absolute non-inferiority margin was 8%, iloperidone would have been shown to be non-inferior to haloperidol. Sensitivity analyses with different responder criteria in the range of 30% change in PANSS suggest that if an absolute non-inferiority margin would be set to 11%, non-inferiority could be concluded.

Although the presented analyses support non-inferiority conclusions for a range of non-inferiority margins, there remain major deficiencies of the analyses: The analyses are not based on randomised groups and all additional analyses performed are post-hoc analyses. Drop out in the initial DB phase until day 42 was 19% (iloperidone) vs. 26% (haloperidol). Although drop out due to unsatisfactory therapeutic effect was similar 8% (iloperidone) and 7% (haloperidol) still bias due to selection cannot be excluded as there was no randomization prior to entry in the subsequent DB phase which lasted until week 52. For the presented post-hoc analyses type I error is not controlled, as would be normally acceptable for demonstration of long-tern efficacy. Therefore it is concluded that for iloperidone long-term efficacy has not been sufficiently demonstrated.

2.5.3. Conclusions on the clinical efficacy

Short-term efficacy has been demonstrated, however a moderate effect and delayed effect and uncertainties due to drop out and heterogeneity in response rate. Long-term efficacy was not sufficiently demonstrated.

2.6. Clinical safety

Clinical safety focuses on the results of 9 controlled studies in adult patients with schizophrenia or schizoaffective disorder. These studies comprise one Phase 2b study (ILP2001), one Phase 2a study (ILO522 2328), and seven Phase 3 studies (ILP3000, ILP3001, ILP3002, ILP3003, ILP3004, ILP3005, and VP-VYV-683-3101). Study ILP2001 is a prospective, randomized, double-blind, multicenter study to evaluate the safety of two titration schedules and to compare the safety and efficacy of bid and qd regimens to haloperidol in patients with schizophrenia. Study ILO522 2328 is a randomized, open-label, multicenter, 5-arm, safety study evaluating the effect of iloperidone at doses of 8 mg bid, 12 mg bid, and 24 mg qd on QTc interval duration in the presence and absence of metabolic inhibition, relative to other antipsychotics in healthy patients diagnosed with schizophrenia or schizoaffective disorder. Further safety information is provided by 28 phase 1 and 2 studies, including safety data from 271 healthy volunteers and 382 patients with schizophrenia, which has not been integrated into the safety data base but described separately (because of totally different data base structure). The cut-off date for clinical safety data was December 4, 2006.

Patient exposure

4439 adult patients with schizophrenia and schizoaffective disorder were enrolled in one of the nine controlled studies receiving at least one dose of the study drug, and were evaluable for safety using the following groups:

Patient exposure in Study Group 1 (all patients in any phase of the nine integrated studies)

3297 of these patients have been exposed to iloperidone during at least one phase of the studies (2070.31 patient-years). Nearly half of the patients received a modal dose of 10-16 mg/day iloperidone, for a cumulative exposure of approximately 1245 patient-years at that dosage.

Approximately half of the patients treated with iloperidone (any dosage) received the substance for more than 3 months, more than one-third received iloperidone for at least 6 months, and about 21.2%

of iloperidone-treated subjects were exposed for 12 months or longer. 24 mg is considered to be the maximum recommended daily dose. 64 patients received iloperidone 20-24 mg/d for more than 6 months and 22 patients for more than 12 months. The duration of patient exposure in the 20-24 mg/d group does only support short-term iloperidone-treatment.

Patient exposure Study Group 2 (patients enrolled in the double-blind phase of the placebo-controlled clinical studies: Studies 3000, 3004, 3005, 3101)

1344 patients were exposed to the double-blind phase of iloperidone for a total duration of 102.42 patient-years. Most of these patients received 10-16 mg iloperidone per day (483 subjects, 41.59 patient-years). The mean duration of iloperidone treatment was 27.8 days with no patient receiving treatment for longer than three months.

Patient exposure in Study Group 3 (patients enrolled in the double-blind phase of the active- or placebo-controlled clinical studies: Studies 2001, 3000, 3001, 3002, 3003, 3004, 3005, 3101)

2764 patients were exposed to the double-blind phase of iloperidone for a total duration of 1019.59 patient-years. 1425 of these subjects received 10-16 mg/day iloperidone, whereas only 14% belonged to the 20-24 mg/day dosage group. The mean duration of iloperidone treatment was 134.7 days.

Patient exposure in Study Group 4 (patients enrolled in the open-label period: studies 2001, 3000, 3001, 3002, 3003, 3004, 3005)

1215 patients were exposed to iloperidone for a combined duration of 1046.12 patient-years. The majority of these patients had also received iloperidone in the double-blind phase (n=788, 752.30 patient-years). The mean duration of open-label iloperidone was 314.5 days. More than 60% of patients received open-label iloperidone for longer than 6 months, and around one-third of patients received iloperidone for longer than 12 months. The open-label phase of study 3101 was ongoing at the time of integrated safety database creation and is therefore not included in the ISS. Of note, the company proposed a post-authorisation measure to pool data into the existing database and report any safety signals in future PSURs, which is acceptable.

Adverse events

Overall rate of adverse events:

Study Group 1:

The frequency of adverse events of iloperidone (84.9%) was similar to those of the active comparators (haloperidol 92.1%, risperidone 81%, and ziprasidone 87%), but higher than with placebo (75.1%).

SOC`s primarily affected, were: Gastrointestinal Disorders, Nervous System- and Psychiatric Disorders. Furthermore, adverse events related to Cardiac Disorders, Infections and Infestations, Dizziness, Psychotic Disorder, Schizophrenia, and Respiratory Disorders were reported more frequently in the iloperidone group compared to the active comparator groups and placebo. Weight increased was reported as an adverse event more frequently in the combined iloperidone group (4.1%) compared with the placebo (0.7%) and haloperidol (0.9%) groups.

A dose-related increase in adverse events in Study Group 1 was obvious for GI-disorders, fatigue, weight increased, dizziness, somnolence, sedation, nasal congestion and tachycardia.

Study Group 2

revealed an overall adverse event profile of iloperidone of 80.7% (data from 1344 treated patients), which is higher compared to placebo (75.1%) and risperidone (78.4%) but lower than ziprasidone (86.7%) and haloperidol (94.9%). Nervous System Disorders were reported at a lower incidence in the

placebo group (35.3%) compared to the combined ILO (44%) and active groups (47.4%-70.3%). Emerge of psychiatric disorders was lowest for ziprasidone (27.3%) and highest in the haloperidol group (56.8%). The occurrence in the combined ILO group was comparable to the placebo group (38% vs. 39.7%) and comparable to risperidone (38.9%). Preferred terms of Extrapyramidal Disorder, Tremor and Akathisia for iloperidone were reported in a similar number compared to placebo. Weight increased was reported as an adverse event more frequently in the combined iloperidone group (3.5%) compared to placebo (0.7%) and haloperidol (0.0%). There was also a dose-related increase in reporting weight gain (0.9%, 1.2% and 9.5% for the ILO 4-8 mg/day, ILO 10-16 mg/day and ILO 20-24 mg/day groups, respectively), with the ILO 20-24 mg/day group also having a higher incidence compared with risperidone (2.6%) and ziprasidone (4.7%).

Study Group 3

revealed an overall incidence of patients with at least one TEAE of 83.6% for the combined iloperidone group compared to 75.1% for the placebo group.

Tachycardia, nasopharyngitis, psychotic disorder, schizophrenia, and nasal congestion occurred with a higher frequency in the combined iloperidone group compared to placebo or any of the active comparators. Dose-related increases in this study group were found for dry mouth, weight increased, heart rate increased, nasal congestion and tachycardia.

In Study Group 4, adverse events were reported by over half of patients, regardless of treatment assignment. The most commonly affected system-organ classes (SOCs) involved Nervous System and Psychiatric Disorders. Adverse event rate of some of the SOCs were lowest in the ILO-ILO group compared to Placebo-ILO, HAL-ILO and RIS-ILO, i.e. cardiac disorders, GI disorders, nervous system disorders, psychiatric disorders.

Adverse events of special interest:

Suicidality has not been formally explored in the phase 2/3 clinical program for iloperidone according to the “Draft guideline on clinical investigation of medicinal products in the treatment of schizophrenia” (CHMP/40072/2010). However, the a priori risk of suicide is high in the target population and therefore detailed and elaborate analysis of fatal suicide cases is considered a crucial part of the application. It should be demonstrated that the risk is comparable or lower as compared to other atypical antipsychotics. Since suicidality-related adverse events occurred with an overall higher incidence in the iloperidone group (four completed suicides) compared to placebo (0), and compared to the comparators (only one suicide in the haloperidol group).

From the assessment of the suicidality analysis it was then concluded that available data do not allow for a comprehensive conclusion, given the relatively limited amount of data, A larger suicide rate was thus reported for iloperidone from clinical trials compared to active comparators (and placebo) while the exposure-adjusted suicide rate based on prescription data referred to by the Applicant, and in comparison with data from the literature, does not confirm an increased suicide rate for iloperidone. However, given the increased clinical risk for lack of efficacy at lower iloperidone dosing regiments and the need for titration and complementary medication during this period, the potential increased risk for suicidality indicated and suicidal ideation cannot be excluded.

Cardiac Safety

Regarding cardiac safety, a thorough QTc study (2328) and QTc evaluation during Phase 3 clinical studies have been submitted as well as QTc prolongation evaluation reported from additional long-term safety studies:

QTc study ILO522 2328

Study objectives and methodology

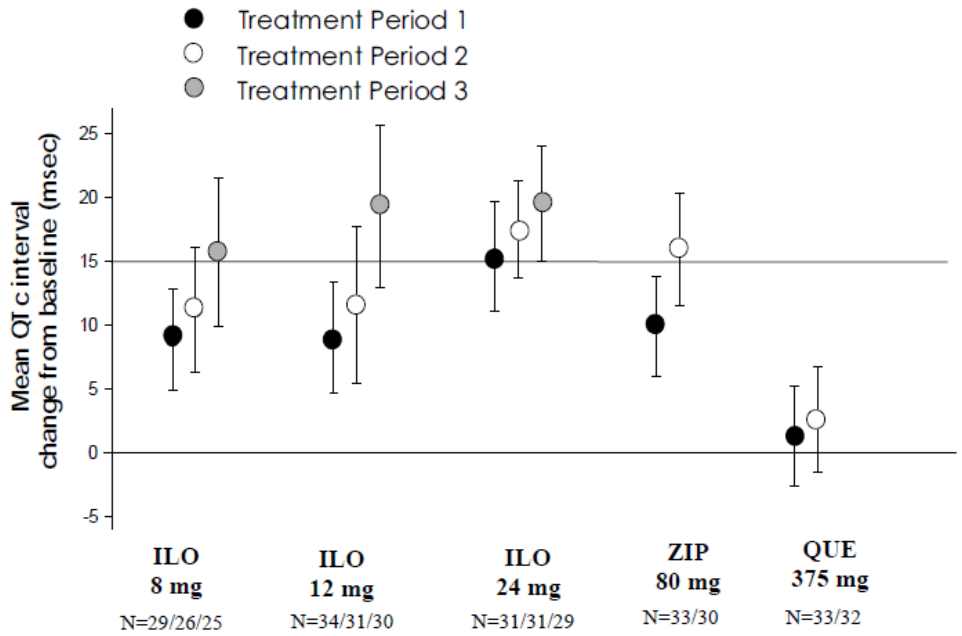
For this study, 242 schizophrenic or schizoaffective patients (male and female), who were otherwise healthy, were screened to receive ILO 8 mg BID, ILO 12 mg BID, ILO 24 mg QD, ziprasidone 80 mg BID (*positive control*) or quetiapine 375 mg BID (*negative control*) in the absence or presence of metabolic inhibition. A negative placebo control is missing. ECGs were recorded on three successive days after steady-state levels were attained (SSD1, SSD2, SSD3). During Treatment Period 2, an inhibitor (paroxetine) of the primary cytochrome P450 isoenzyme (2D6) was added to each arm. During Treatment Period 3, only iloperidone patients received ketoconazole in addition to paroxetine for 2 days before ECG assessments were conducted. Study objective was to evaluate the effects of steady-state concentrations of iloperidone on QT prolongation in patients with schizophrenia (otherwise healthy). Changes in QTc were measured at t_{max} during 3 periods (dose escalation – metabolic inhibition with paroxetine – metabolic inhibition with ketoconazole) compared to baseline. Three ECGs were conducted at each steady-state day (SSD).

Results

Iloperidone was found to be associated with prolongation of the QTc interval (mean change: 8.9 – 15.4 msec without inhibitor) with the highest effect seen in the 24 mg QD group (higher plasma concentrations of iloperidone and its metabolite P88). Mean change from baseline in QTcF at t_{max} for ILO 8-12 mg BID doses was similar to ziprasidone 80 mg BID.

Metabolic inhibition of the one or both CYP pathways, 2D6 and 3A4, enhanced the effect on increasing plasma concentrations and QTc prolongation among iloperidone-treated patients and led to seven patients with a QTcF interval change of 60 msec and more.

Figure S1. Mean QTc (Fridericia) Change (95%CI) from baseline to steady state at t_{MAX}* during Treatment Periods 1, 2, and 3 (Secondary QTc Population)



ILO=iloperidone; ZIP=ziprasidone; QUE=quetiapine

P1=Period 1, P2=Period 2, P3=Period 3. Note: * t_{MAX} = estimated time of maximum concentration (ILO=2-4 hours post-dose; ZIP=5-7 hours post-dose; QUET= 1-2.5 hours post-dose).

Treatment Period 1 (without inhibitor): Mean QTcF change was similar for iloperidone 8 mg BID (8.5+10.5 msec), iloperidone 12 mg BID (9.0+12.5 msec), and ziprasidone 80 mg BID (9.6+11.0

msec). Quetiapine 375 mg BID (1.3+11.1 msec) was associated with the smallest mean change from baseline at t_{max} in QTcF and iloperidone 24 mg QD (15.4+11.7 msec) was associated with the largest mean change from baseline at t_{max} in QTcF.

- The number of patients (%) with any QTcF increases of > 30 msec from baseline to steady state during Treatment Period 1 was greatest in the iloperidone 24 mg QD [19 (61%)] group followed by the ziprasidone 80 mg BID [17 (52%], iloperidone 12 mg BID [15 (44%)], iloperidone 8 mg BID [9 (31%)] and quetiapine [4 (12%)] groups, respectively.
- Two patients in Treatment Period 1 experienced increases in QTcF of > 60 msec from baseline to steady state at t_{max}. One patient was in the iloperidone 8 mg BID group and the other was in the iloperidone 24 mg QD group.

Treatment Period 2 (the presence of one metabolic inhibitor): The mean change in QTcF from baseline to steady state at t_{max} was highest in the iloperidone 24 mg QD (17.5+10.3) and ziprasidone 80 mg BID (15.9+11.8) groups followed by the iloperidone 12 mg BID (11.6+16.8) and iloperidone 8 mg BID (11.2+12.0) groups. The smallest mean change was observed in the quetiapine 375 mg BID (2.6+11.5) group. In comparison to Treatment Period 1, the mean change QTcF at t_{max} was numerically higher in all treatment groups.

- The number of patients (%) with any QTcF increases of > 30 msec from baseline to steady state at t_{max} was greatest in the iloperidone 24 mg QD [22 (71%)] group, followed by the ziprasidone 80 mg BID [18 (60%], iloperidone 8 mg BID [14 (54%)], iloperidone 12 mg BID [15 (48%)], and quetiapine [6 (19%)] groups, respectively.
- Two patients in Treatment Period 2 experienced increases in QTcF of > 60 msec from baseline to steady state at t_{max}. One patient was in the iloperidone 8 mg BID group and the other was in the iloperidone 24 mg QD group.

Treatment Period 3 (in which a second metabolic inhibitor was added to the regimen of iloperidone-treated patients): Mean change in QTcF from baseline to steady state at t_{max} was highest in the iloperidone 24 mg QD (19.5+11.9) and iloperidone 12 mg BID (19.3+17.1) groups followed by the iloperidone 8 mg BID (15.7+14.1) group.

- The number of patients (%) with any QTcF increases of > 30 msec from baseline to steady state at t_{max} was greatest in the iloperidone 24 mg QD [21 (70%)] and iloperidone 12 mg BID [20 (69%)] groups followed by the iloperidone 8 mg BID [13 (52%)] group.
- The proportion of patients with QTcF increases of > 30 msec at t_{max} in the iloperidone 8 mg BID and 24 mg QD treamtent groups was similar to that observed in Treatment Period 2.
- The proportion of patients with QTcF increases of > 30 msec at t_{max} in the iloperidone 12 mg BID was greater in Treatment Period 3 than in Treatment Period 2.
- Four patients in Treatment Period 3 experienced increases in QTcF of > 60 msec from baseline to steady state at t_{max}. One patient was in the iloperidone 8 mg BID group and the other 3 patients were in the iloperidone 12 mg BID group.

No patient was found to exhibit values of more than 500 msec.

Of note and concern is an observed mean change in heart rate during treatment period 2 and 3 (under metabolic inhibition): heart rate slightly increased during the first period with iloperidone and no metabolic inhibition (mean change from baseline 7.6, 7.7 and 5.3 bpm for iloperidone 8 mg BID, 12 mg BID and 24 mg QD). During treatment period 2 and 3, the mean heart rate decreased significantly about – 0.9, -3.9, and -4.8 bpm and -1.6, -4.7, and -5.2 bpm for the three dose regimens.

There was a high rate of patients having at least one adverse event during this study (88 % for ILO 8 mg BID, 97% for ILO 12 mg BID, 91% for ILO 24 mg QD, 91% for ziprasidone 80 mg BID, and 86% for quetiapine 375 mg BID). The most frequently affected SOC`s were Nervous System, GI- system and Psychiatric Disorders. Eight patients from the ILO 12 mg BID group (22%) had an adverse event deriving from Cardiac Disorders; whereas the incidence of these events was much lower in the other groups. Seven of these eight patients suffered from Tachycardia. In the ILO 8 mg BID group, one patient had a serious adverse event of supraventricular tachycardia. 2 patients discontinued the study because of tachycardia.

QTc evaluation during Phase 3 clinical studies

Analysis of mean QTcF changes over time revealed a slight time-dependant increase for the combined iloperidone group from week 4 on up to more than 12 months of treatment. This effect could not be seen in the active comparator groups.

A total of 2.3% of patients in the combined iloperidone group had a QTcF value of ≥450 msec, which was more pronounced in females. Two patients, both males, had QTcF values above 500 msec. These incidences are not considered to be related to the study drug, since one patient took an overdose of iloperidone and the other patient had several comorbidities.

Further concern was raised with regard to sex differences. A total of 4.3% of female patients had a QTcF interval ≥450 msec in the combined ILO group compared to 1.3% in males.

The applicant clarified and presented shift tables showing shifts from normal (abnormal) baseline values in QTc to normal (abnormal) values during treatment. Using this approach, 0.6% of males and also 0.6% of females in the iloperidone combined group, who had a QTcF value <450 msec (<470 msec) at baseline had a maximum QTcF value ≥450 msec (≥470 msec) post-treatment. 0.3% of males (0.6% of females) in the iloperidone 10 – 16 mg/day group who had a QTcF value <450 msec (<470 msec) at baseline had a maximum QTcF value ≥450 msec (≥470 msec) post-treatment.

Exposure (adjusted to body weight) to iloperidone, P88 and P95, was reported to be nearly 50% higher in females than in males based on the population pharmacokinetic analysis After having evaluated the applicant´s response, no firm conclusions with respect to pharmacokinetic gender differences can be drawn. Taking these findings together, a pronounced cardiovascular risk in females cannot be ruled out.

A proarrythmic concern has to be raised for QTc interval increases of more than 60 msec. QTcF increases of ≥15% and ≥60 msec from baseline yielded similar results of up to 8.3% of iloperidone-treated patients and only half of this number in ziprasidone-treated patients. QTcF increases of ≥30 msec were even detected in nearly 40% of iloperidone treated patients, which is largely in accordance with the results from the thorough QT study 2328.

A further contribution to the QTc prolonging effect of iloperidone is the metabolism via CYP2D6. Iloperidone is extensively metabolised via hydrolysis and CYP2D6 resulting in the two main metabolites, P88 (active) and P95 (inactive). Therefore, QTc interval prolongation may be triggered by metabolic inhibition and cytochrome polymorphisms, which was also examined in study 2328 and study 3101. Additionally to the results already described for study 2328, 128 patients consented to a pharmacogenetic substudy and were genotyped for 2 common CYP2D6 single-nucleotide polymorphisms [*4 (G1846A) and *10 (C100T; a.k.a. P34S)] to determine if either is associated with an increased risk for QT prolongation after treatment with iloperidone. Poor and intermediate metabolizers had larger increases in QTcF interval from baseline following treatment with iloperidone compared with patients who possess the wild type allele during Period 1 (up to 31.3 msec). Therefore it is proposed to administer reduced doses in intermediate and poor metabolizers. To minimise the risk for QT prolongation, mandatory genotyping of CYP 2D6 for any patient dosed above 6 mg BID was

proposed with subsequent lower dosing recommendations targeting 6-8mg, depending on the CYP2D6 genotype status.

QTcF data were calculated on a subset of patients in study 3101, who had the CYP2D6*4 (1846GA or AA) or CYP2D6*10 (100CT or TT) polymorphisms. In the iloperidone group, mean changes in QTcF interval from baseline at Day 14, Day 28 and endpoint were significantly higher in the combined non-GG subgroups compared with the GG (wildtype) subgroup. CYP2D6*4 polymorphisms did not play a role for ziprasidone, since it is metabolized via CYP3A4.

Concerning ECG abnormalities in clinical Phase 3 studies, Study Group 1 revealed a similar number for placebo-, haloperidol-, and risperidone-treated patients (15.5%, 17.3%, and 12.7%), whereas these abnormalities happened in 22.3% of patients in the combined iloperidone group and in 31.3% in the ziprasidone group. Among the 3 iloperidone dose groups, there was a dose-related increase in the ILO 20-24 mg/day group (32.7%) compared with the placebo group (15.5%) and the 2 lower dose groups (18.7% and 21.9% for ILO 4-8 and 10-16 mg/day, respectively). In Study Group 2, 18.1% of patients from the combined ILO group showed ECG abnormalities compared to 15.5% in the placebo group. The occurrence in the active comparator groups was 8.3% to 31.8%.

Cardiac adverse events occurred in a similar number in iloperidone- and ziprasidone-treated patients (9.2% and 11.4%), which was higher than in patients from the placebo, haloperidol and risperidone group (3.9%, 4.2%, and 3.5%). The highest frequency of serious cardiac AE was reported in the combined ILO group (0.7%), as well as the number of deaths due to cardiac AE (3 deaths). One death was reported in the placebo group due to cardiac AE. Among the three iloperidone dose groups, cardiac adverse events were reported more frequently in patients receiving ILO 20-24 mg/day (19.2%) than either of the 2 lower doses (7.5% each). Tachycardia was reported most frequently in the combined ILO group (3.4%) vs. placebo (0.9%). According to the dose administered, the percentage of tachycardia in the ILO 20-24 mg/d arm was nearly four times higher than in the lower dose groups. In the placebo-controlled studies, Tachycardia was reported to appear in a high percentage of subjects in the combined ILO group compared to placebo (4.2% vs. 0.9%). This number was even twice as high as in the ziprasidone group (2%).

QTc prolongation reported from additional long-term safety studies

Two additional long-term safety studies were included in the application comparing iloperidone (4-16 mg/d) to haloperidol (5-20 mg/d) in Study ILP3004LT, and to risperidone (2-8 mg/d) in Study ILP3000LT).

Study ILP3000LT: The mean change in QTc interval from baseline to endpoint at Week 52 was higher in the iloperidone group than in the haloperidol group (9.1 msec vs. 4.0 msec); however, there were no treatment-emergent adverse events in the iloperidone group related to QTc changes. The evaluation of the safety results were hampered by the low number of patients concluding the study and the limited number of available ECG assessments that was much lower for the haloperidol group (n=5) than for the iloperidone group (n=33).

Study ILP3004LT: The mean change in the QTc interval from baseline to Week 52 was higher in the iloperidone group (14.4 msec vs. 7.8 msec) for the risperidone treatment group.

Given the discontinuation rate was high in both of these studies and for all treatment groups, the validity of the results was limited as for conclusions to be drawn from the results. However, QTc prolongation in the iloperidone treatment groups exceeded that for the haloperidol and risperidone treatment groups. In Summary:

- QTc study ILO5222328 revealed mean prolongation of QTc interval of 8.5 msec without metabolic inhibition, which increased to approximately 16 msec under full metabolic inhibition (CYP2D6 and CYP3A4) in dosages of 8 mg BID.

- At the same time 31% of subjects were reported to have a QTc interval increase of more than 30 msec in any of 9 consecutive ECG measurements without metabolic inhibition, increasing to 52% of subjects with CYP2D6 and 3A4 metabolic inhibition.

- Decrease in heart rate was observed under metabolic inhibition (CYP2D6 and/or CYP3A4 inhibition) up to a mean of -5.2 bpm.

- KCNQ1 polymorphic gene (contributing to long QT syndrome) may have much higher influence on QTcF interval changes compared to genetic polymorphism of CYP2D6 and lead to highest QT prolongation in combination with CYP2D6 polymorphism (up to 26 msec).

- In the phase 3 clinical studies, a slightly time-dependant increase in QTc interval prolongation was seen.

- QTcF increases of ≥15% and ≥60 msec from baseline yielded similar results of up to 8.3% of iloperidone-treated patients and only half of this number in ziprasidone-treated patients. QTcF increases of ≥30 msec were even detected in nearly 40% of iloperidone treated patients.

- QTc interval prolongation was nearly twice as high for iloperidone compared to risperidone (mean change: 14.4 msec vs. 7.8 msec) and haloperidol (mean change: 9.1 msec vs. 4.0 msec) in long-term studies ILP3000LT and ILP3004LT with doses of 4 to 16 mg/d

Hypotension and orthostatic hypotension

The overall incidence of the AE of orthostatic hypotension and hypotension was higher in iloperidone-treated patients (3.0% and 1.7%) compared to placebo and the active comparators. The majority of hypotensive events in iloperidone-treated patients occurred during Week 1.

Seizures

The potential of iloperidone for producing seizures is low. 13 patients from the combined ILO group had seizure as AE (0.4%). This was in the same range for placebo, haloperidol, and risperidone. No patient developed seizures under ziprasidone.

Extrapyramidal symptoms

18.7% of patients in the combined iloperidone group in Study Group 1 had an extrapyramidal-related adverse event sometime during treatment, which was higher compared with placebo-treated patients (11.6%). Nevertheless, extrapyramidal-related AE occurred in a higher frequency in the haloperidol, risperidone, and ziprasidone group (59.7%, 29.9%, and 24.5%). This result was corroborated by evaluating changes from baseline in EPS rating scale scores and in accordance with evaluation from Study Group 2 (15.6% for the combined ILO group). Taking into account, that haloperidol was administered in doses of up to 20 mg/day the relatively high number of patients suffering from EPS-related adverse events (59.7%) may be partly explained by a high haloperidol dosage.

Prolactin-related adverse events

Only one prolactin-related adverse event was reported from phase 3 studies. The percentages of patients who had a normal prolactin value at baseline and an elevated prolactin value during treatment are as follows: 4.5%, 18.8%, 72.5%, 91.0%, and 10.3% for the placebo, combined iloperidone, haloperidol, risperidone, and ziprasidone groups, respectively.

Glucose-related events

Integrated analysis comprised fasted and fed measurements, which is considered a shortcoming. Fasting glucose was only recorded in Study 3101. Data indicate an overall iloperidone glucose profile comparable to risperidone. Adverse events related to increased glucose were reported for 35 patients (1.1%) in the combined ILO group (Study Group 1), one patient each in the placebo, haloperidol and ziprasidone group, and in two patients from the risperidone group, similar to the other study groups. 5 patients in the combined ILO group (0.2%) suffered from a severe AE. One death was reported in Study Group 1 related to a hyperglycaemic AE (uncontrolled diabetes, Study 3003). The incidence of hyperglycaemia was 0.4% and 1.2% for the >6-12-month and >12-month periods compared with 0.1% to 0.2% for all previous observation periods (except during Weeks 3-4, when it was 0.3%) in Study Group 1. Hence, hyperglycaemia emerges in later stages during treatment with iloperidone.

Schizophrenia-related AE`s occurred in a comparable high rate for the combined ILO and the haloperidol group (39.6% and 40.3%), and a lower rate in the other groups (placebo: 28.6%, risperidone: 30.5%, and ziprasidone: 14.7%). Serious drug-related AEs related to schizophrenia were highest in the combined ILO group (1.2%) compared to all other treatment groups.

Adverse Events by Severity

For the overall study population (Study Group 1), the majority of adverse events across treatment groups were mild to moderate in severity. Severe adverse events were reported in 20.6% of iloperidone-treated patients. This was higher than that observed for the comparator groups (8.2% to 15.1%), except for haloperidol (30.0%). However, the majority of severe adverse events occurred in only 1 or 2 patients per treatment group.

The most commonly reported severe events in iloperidone-treated patients (>1%) all occurred in the Psychiatric Disorder SOC and included psychotic disorder, schizophrenia (all types combined), agitation, anxiety and insomnia. There did not appear to be a dose-related increase in these events among the 3 iloperidone dose groups. The only common adverse event that was reported as severe more frequently in the combined iloperidone group compared with the placebo group (as well as the risperidone and ziprasidone groups) was psychotic disorder.

Serious adverse event / deaths / other significant events

The occurrence of serious TEAEs in Study Group 1 was twice as high in the combined ILO group (19.4%) compared to placebo (8.3%), and decreased to 6.5% in Study Group 2 for the combined ILO group. Nevertheless, the highest rate of serious adverse events across study groups 1 to 3 was observed for ILO 10-16 mg/d, which is part of the target dose of 12-24mg/d. Nervous System Disorders and Psychiatric Disorders were reported most frequently as serious adverse events, among the term “Psychiatric Disorders”, schizophrenia, psychotic disorder and suicidal ideation were mentioned with the highest frequency. Suicidality was not explored for iloperidone according to the “Draft guideline on clinical investigation of medicinal products in the treatment of schizophrenia” (CHMP/40072/2010). Since suicidal ideation was among the most frequently reported serious adverse events, and four suicides occurred in the iloperidone group, there is a considerable concern and need for vigilance follow-up.

Syncope and Torsade de Pointes are considered serious adverse events, which would support a cardiac concern. Syncope was reported for four patients belonging to Study Group 1 (0.1%, all in the dosing group 4-8 mg/d).

In total, 24 patients died while participating in the iloperidone clinical program. Nineteen of these deaths (15 iloperidone, one placebo, three active-controls [two risperidone, one haloperidol]; including

treatment-related and unrelated to treatment) are captured in the safety database. Overall, 16 deaths were recorded under iloperidone treatment during all studies. All deaths occurring on-study or post-study have been judged as *not* related to iloperidone as study medication by the investigators except for one death in Study 3002 (patient 056-1012, reported as “Sudden Death”). Six of the deaths, which occurred under iloperidone treatment, are suspected to be cardiac-related (3001: cardiac failure; 3002: sudden death; septicaemia leading to shock and silent myocardial infarction; 3003: cardio-respiratory detention; 3005: sudden cardiac arrest with respiratory failure; 3101: sudden death [patient 112-0009]).

Another death case occurred in study 3003, which was reported as probable pyloric obstruction and death from pylorus occlusion. This death is - according to the assessor – also suspect of cardiac relation, since the female patient received the substance cisapride over a long time for gastritis. Cisapride is known to prolong the QTc interval substantially, therefore, this death is more supposed to be the fatal outcome of a pharmacodynamic drug-drug interaction of two strong QTc prolonging agents rather than a death resulting from pylorus occlusion. According to the information provided by the company, four of the cardiac-related deaths may be considered “Sudden Deaths”.

Four completed suicides have been reported in subjects assigned to iloperidone treatment. These subjects received 8-16 mg iloperidone per day and were all from the schizophrenic population. Three subjects were below 50 years of age and one was 59 years old. An exacerbation of the underlying psychiatric disorder is most likely to be seen as the cause of these suicides. Nevertheless, suicidality analysis was not conducted and the a priori risk of suicide is high in the target population. Therefore, detailed and elaborate analysis of fatal suicide cases is considered a crucial part of the application. The absence of data evaluating the suicidal potential of iloperidone is a concern. It should be demonstrated that the risk is comparable or lower as compared to other atypical including close monitoring in PSURs.

Mortality analysis per 100 patient years revealed an iloperidone rate lower or similar to placebo treatment or active comparators. The rate of sudden unexpected deaths is lower for iloperidone compared with other marketed antipsychotics. However, sudden death cases under iloperidone treatment during the clinical program as well as postmarketing in the US in combination with the observed dose-dependent QTc prolonging potential of iloperidone still constitute a major safety concern.

Laboratory findings

The effects of iloperidone on the results of biochemistry and haematology laboratory tests (including liver and renal function tests, serum lipid levels, and glucose levels) did not raise any clinically relevant concerns. Iloperidone treatment was associated with minimal increases in alkaline phosphatase and SGPT (ALT) concentration compared with placebo. Of note, more than or equal to fivefold elevation above the upper limit of normal (ULN) for alanine aminotransferase (ALT) was seen in iloperidone-treated patients compared to placebo.

Iloperidone influences prolactin concentration, which is considered a class effect. Prolactin elevations were less pronounced in iloperidone-treated patients compared to risperidone- and haloperidol-treated patients. Therefore, no new safety concern is raised concerning serum prolactin increases. The clinical significance of total cholesterol elevation seems also be negligible, since there were no marked changes in HDL, LDL or triglycerides.

Electrolytes included calcium, chloride, bicarbonate (CO2), inorganic phosphorous, magnesium, potassium and sodium. There were no inter-group differences between iloperidone and placebo in changes from baseline to endpoint or worst value for any electrolytes in any of the treatment groups. Electrolyte imbalance, in particular K, Mg and Ca-concentrations with potential pro-arrhythmic effects,

were specifically examined. The results indicated that iloperidone does not induce changes in electrolytes associated with cardiac arrhythmias.

Abnormal changes in pulse rate were defined as ≥120 bpm and an increase of ≥15 bpm: In Study Group 1 [Study Group 2], 24.3% [29.2%] of patients in the combined ILO group fulfilled this criteria compared to 6.7% [6.7%] of placebo-treated subjects. A similar high rate was detected in the risperidone group (22.9%) [21.9%]. Data from Study Group 4 suggested, that pulse rate elevations are less pronounced during long-term treatment. Nevertheless, pulse rate increases in a high number of iloperidone-treated patients is concerning against the background of cardiac effects of iloperidone.

Iloperidone poses alpha adrenergic properties. Therefore, emerge of adverse events of orthostatic hypotension and syncope could be expected. Looking at the placebo-controlled Study Group 2, orthostatic hypotension was reported in 1.2% of placebo-treated subjects compared to 3.3% of iloperidone-treated patients. Orthostatic hypotension seemed to occur dose-related. Syncope was mentioned for 4 subjects from Study Group 1 as serious adverse event in the combined iloperidone group.

Body weight changes for Study Groups 1 and 2 were also highest in the combined iloperidone group and slightly increased over time. A weight change of 7% and more was reported in 23.2% patients of the combined ILO group of Study Group 1 but only in 13.5% of patients from Study Group 2 and in 4.3% of placebo-treated patients (5.3% to 17.6% for active comparators of Study Group 1 and 5.1% to 11.9% of Study Group 2).

Safety in special populations

The safety of iloperidone was evaluated by age, sex and race.

- Age group analysis was done by separation of the two categories: <50 and ≥ 50 years. 86% of 3210 iloperidone-treated patients were under the age of 50 and 14% were 50 years and older. No patient was 75 years of age or older. Adverse event rate and serious adverse events were similar between the age groups for Study Group 1. Nevertheless, death occurred in a higher percentage in patients 50 years and older (1.3%) versus the younger ones (0.3%). Single adverse events occurred in a similar percentage in both groups. The incidence of anaemia and urinary incontinence was higher in iloperidone-treated patients 50 years or older than in the <50 yrs age group and was also higher compared with patients 50 years or older in comparator groups for all 3 study groups. Tachycardia was more common (two-fold) in iloperidone treated patients below 50 compared with patients 50 years or older with a reverse trend observed for the active comparators. This possibly reflects the receptor binding profile of iloperidone.

Increased incidence of Gastrointestinal Disorders, Infections and Infestations, Respiratory Disorders was observed in the Age Category >50 Years. The only individual serious adverse events that exhibited an apparent age-related increase among iloperidone-treated patients (>50 yrs) occurred in the Psychiatric disorder SOC and included depression and schizophrenia paranoid type.

Elderly Patients with Dementia: Study ILP3007 Part 1 and Part 2 evaluated the safety and tolerability of iloperidone in treating psychotic and behavioural symptoms in elderly patients (60 to 90 years) with dementia. The mean maximum dose of study drug received during the treatment period was 2.3 mg/day in the iloperidone group and 1.4 mg/day in the risperidone group. The mean modal dose of study drug during the treatment period was 1.9 mg/day in the iloperidone group and 1.2 mg/day in the risperidone group.

Three deaths (2 iloperidone, 1 risperidone), none of which was considered related to study drug, were reported. No new adverse events occurred in elderly patients that have not been previously reported in

young patients with schizophrenia treated with iloperidone. None of the patients had clinically relevant laboratory abnormalities. Iloperidone was not associated with a clinically significant increased risk of vital sign or ECG abnormalities, or incidence of extrapyramidal symptoms.

- Gender: Of the 3210 iloperidone-treated patients, 66% were male and 34% were female. A noteworthy difference between male and female was the occurrence of serious adverse events (17.9% in males and 22.4% in females. This became obvious in the 24 mg iloperidone dose group but not for the 2 lower iloperidone dose groups (mainly due to a higher incidence of serious psychiatric events). In contrast, a higher percentage of males than females were reported for schizophrenia related serious events in the active comparators haloperidol and risperidone.

- Race: The safety profile was not significantly affected by results of racial comparison.

- Patients with mild or moderate hepatic impairment: Study ILO522 0103 (open-label, parallel group study) evaluated the effects of a single, 2 mg-dose on patients with mild to moderate hepatic impairment (4 subjects each). Dose is not in line with clinical doses and therefore, results are of limited validity. No deaths or serious adverse events occurred during this study. Adverse events reported were largely in line with those reported from healthy subjects. Exposure to iloperidone is not different. Metabolism of iloperidone to metabolite P95-12113 is decreased compared to healthy subjects, whereas metabolism and exposure to the active metabolite P88-8991 is higher (up to 50%) in hepatically impaired subjects. .Plasma protein binding of iloperidone is not significantly altered in mild to moderate hepatic impaired subjects.

- Patients with severe renal impairment: Study ILO522 0102 (open-label, parallel group study) evaluated the effects of a single, 3 mg dose on patients with severe renal impairment. Renal elimination of parent iloperidone was found to be less than 1% of the orally administered dose. No clinically significant effect of renal dysfunction on iloperidone disposition was found. The disposition profile of active metabolite P88-8991 is similar between healthy subjects and renally impaired subjects, although unbound concentrations are not available and individual data show quite extensive exposure increase of P88. Inactive metabolite P95-12113 showed higher exposure and lower clearance in renally impaired subjects. As a consequence, this metabolite could accumulate upon chronic dosing of iloperidone warranting a closer monitoring of those patients.

- Use in Pregnancy and Lactation: There were 5 pregnancies in subjects who received iloperidone across all clinical studies. Two were ectopic pregnancies, resulting in abortions and complete recoveries of the patients. Two patients had normal deliveries, with healthy infants. The fifth pregnancy ended in spontaneous abortion, followed by complete recovery of the patient; no relationship to study medication was suspected.

Safety related to drug-drug interactions and other interactions

Drug interaction trials

- Study ILO0522 0104 was an interaction trial with dextromethorphan as a CYP 2D6 substrate using a two-cohort, randomized, open-label, three-period crossover design with 19 healthy subjects genotyped as extensive metabolizers and 8 subjects genotyped as poor metabolizers. Study objectives included evaluation of any differences between metabolism of 2D6 extensive metabolizers and poor metabolizers since this isoenzyme plays a central role in iloperidone metabolism. Furthermore, dextromethorphan serves as a prototype substrate for 2D6, indicating potential drug-drug interactions. As a result to be expected exposure to iloperidone and its metabolite P88 were significantly increased while exposure to metabolite P95 was significantly decreased in poor CYP 2D6 metabolizers. Dextromethorphan as a CYP 2D6 substrate did not alter the metabolism of iloperidone in extensive metabolizers.

- Study ILO0522 0108 evaluated the potential drug-drug interaction of iloperidone and fluoxetine for two reasons: (1) competitive metabolic inhibition between iloperidone and fluoxetine via CYP 2D6 is possible and (2) fluoxetine may be co-administered in schizophrenic patients. Steady state conditions of fluoxetine and its metabolite have to be ensured by administration for 28 days (fluoxetine and norfluoxetine have long half-lives). On day 29, a single 3mg-iloperidone dose was given to healthy subjects. Exposure to iloperidone and P88 was significantly increased ($AUC_{0-\infty}$ by 131%, C_{max} by 70% for iloperidone and by 119% and 64%, respectively, for P88) following concomitant administration of iloperidone and fluoxetine. At the same time, exposure to P95 was significantly decreased ($AUC_{0-\infty}$ by 53%, C_{max} by 70%), indicating inhibition of the CYP2D6 metabolic conversion of iloperidone to P95. Iloperidone did not alter the pharmacokinetics or metabolism of fluoxetine and norfluoxetine. No serious adverse events occurred during the study and common adverse events were in a similar incidence compared to other phase 3 studies.
- Study ILO0522 0107 explored the potential drug-drug interaction of iloperidone via the CYP 3A4 metabolic pathway using ketoconazole as a potent CYP 3A4 inhibitor. 19 subjects were randomly assigned to receive either a single 3-mg dose of iloperidone or ketoconazole 200 mg BID for four days (8 doses), with a single 3-mg dose of iloperidone co-administered with the 7^{th} dose of ketoconazole on Day 4. As a result, coadministration led to a 50% increase in iloperidone exposure. Exposure to P88 and P95 increased by 40-60%. No deaths or serious adverse events were reported during this trial. However, 18 from 19 subjects reported adverse events (79% of the subjects reported adverse events while receiving iloperidone alone and 90% reported AEs while receiving the combination).

Discontinuation due to adverse events

Overall discontinuation rate in the combined iloperidone group was 32.5% in the short-term phase, 54.5% in the long-term phase and 46.0% in the open-label phase regardless the reason for discontinuation. Discontinuation rate in patients receiving placebo was 52.5% (only the short-term phase was placebo-controlled).

7.5% of patients belonging to Study Group 1 experienced an adverse event leading to permanent drug discontinuation from the combined ILO treatment compared to 5.5% in the placebo group. The incidence in the risperidone, haloperidol and ziprasidone group was similar. Among the three iloperidone dose groups, a dose related decrease in discontinuation rates due to adverse events could be seen (10.4%, 5.7% and 5.5% in the ILO 4-8, 10-16, and 20-24 mg/day groups). 1.6% in the combined ILO group discontinued treatment due to an adverse event belonging to Nervous System Disorders, similar to the placebo rate (1.0%), and lower compared to those who received haloperidol (5.9%), risperidone (3.2%) or ziprasidone (3.8%). Discontinuation in the combined ILO group due to Psychotic Disorder was 2.5%, similar to placebo, haloperidol and risperidone (2.6%, 2.4%, and 1.9%), and lower than ziprasidone (4.3%).

Cardiac disorder as reason for discontinuation was highest in the combined ILO group (0.8% versus 0.3% for placebo, 0.2% for haloperidol, 0% for risperidone, and 0.5% for ziprasidone) and General disorders and administration site disorders (0.7% versus 0.2% for placebo, 0.4% for haloperidol, and 0.6% for ziprasidone).

In Study Group 2, adverse events led to permanent discontinuation of treatment in 5.1% of iloperidone-treated patients. This was lower than that observed for the other treatment groups (6.2% to 10.7%), and for placebo (5.5%). Among the three iloperidone dose groups, there was a dose-related decrease in the overall percentage of patients with adverse events leading to discontinuation. Again, the SOC with the highest percentage of discontinuation was Psychiatric Disorders (1.5% for iloperidone-treated patients). Study Group 3 showed similar results.

In Study Group 4, adverse events led to permanent discontinuation of treatment in 4.1% of ILO-ILO treated patients. This was lower than that observed for the other treatment groups (7.6% to 10.6%), except for HAL-ILO (3.2%).

Post marketing experience

Iloperidone was introduced in the US in 2009 but and is now marketed in Argentina and Israel, too. Postmarketing data (Periodic Safety Reports, to be raised quarterly) are available from 6th of May 2009 up to 05th of May 2012 for an estimated 12,000 patients in the United States. These data have not been included in the integrated safety database. Overall review of postmarketing data for iloperidone identified 20 cases of deaths (see table S1).

Table S1: Death cases reported during postmarketing observation (cut off date: May 2012)

Subject ID	Description	Past Medical History	Remarks
US01745	62-year old male, severe depression, two days after starting titration pack, patient was found unconscious in cardiac arrest	Coronary artery bypass graft with associated congestive heart failure	Sudden death
US31091	61-year old female; iloperidone 10mg BID for one month; normal ECG 2 weeks prior to death	Diabetes, hypertension, COPD, cardiomegaly	Sudden death
US87695	41-year old female; iloperidone 10 mg BID; found dead in bed		Sudden death
US50772		Cardiovascular disease, hypertension, obesity	
US02794		Drug and alcohol abuse (jail)	
US66635	55 year-old male; starting with iloperidone titration pack (2 mg BID); patient collapsed at wheel and died on scene of car accident of myocardial infarction	Coronary artery disease, angina, COPD, obesity	Sudden death
US29816	35 year-old, gender unknown; iloperidone 6 mg BID; found dead in bed; concomitant medication was ziprasidone and valproic acid	Autism; tendency for arrhythmias	Sudden death
US17434	42 year-old male on iloperidone 12 mg BID; sudden death	Drug abuse, bipolar disorder; superior sinus thrombosis	Sudden death
US07138	31 year-old male on iloperidone 6 mg BID for two months; developed priapism, started risperidone,	Alcohol abuse	

	later switched to asenapine and died of pulmonary embolus		
US12001	Patient died in clinic		
US002681	Male patient on iloperidone 1 mg; suicide after stopping treatment	Drug abuse	
US002896	46 year-old male on iloperidone 12 mg BID; sudden death three months later		Sudden death
US52863	Single car accident or suicide		
US59578	Female on 8 mg iloperidone BID (depression); witnessed to collapse by her husband and died		Sudden death
US63566	Underlying cancer		
US17890	53 year-old female died of pulmonary embolism; iloperidone 6 mg BID		
US004856	No details of death available		
US006237	46 year-old female on iloperidone 6 mg, no details of death		
US006164	50 year-old male on iloperidone 8 mg, no details of death		
US007919	42 year-old female on iloperidone 3 mg, died in sleep	Sleep apnea	

“Sudden death” could initially be indicated in eight patients according to the applicant. In one case with unknown cause (US02794), a possible cardiac relationship cannot be ruled out.

Following Oral Explanation in November 2012, the applicant reclassified three of the post-marketing SUDs as non-SUDs (US01745, US31091, and US66635). According to the applicant, these patients had a cardiovascular disease history for which death could somehow be expected. Since information on these deaths is scarce and no new data have been provided, the CHMP still considers these deaths to be SUDs as in the first classification for the reason that all deaths were “sudden” in nature under iloperidone treatment.

2.6.1. Discussion on clinical safety

The integrated safety database for iloperidone consists of nine controlled studies in adult patients with schizophrenia or schizoaffective disorder, including one Phase 2b, one Phase 2a, and seven Phase 3 studies. Additional data derived from 28 Phase 1 and 2 studies not included in the integrated safety database. These additional studies revealed a similar safety profile of iloperidone as depicted in the nine controlled studies. The studies comprised a mixed population consisting of schizophrenic and schizoaffective patients.

4439 patients in total were enrolled in one of the nine controlled studies. Results were presented separately for four study groups consisting of Study Group 1 (all patients in any phase of the nine

integrated studies), Study Group 2 (patients enrolled in the double-blind phase of the placebo-controlled clinical studies 3000, 3004, 3005, 3101), Study Group 3 (patients enrolled in the double-blind phase of the active- or placebo-controlled clinical studies 2001, 3000, 3001, 3002, 3003, 3004, 3005, 3101), and Study Group 4 (patients enrolled in the open-label period, studies 2001, 3000, 3001, 3002, 3003, 3004, 3005). Patients were grouped to three different dose ranges for iloperidone (4-8 mg/d, 10-16 mg/d, and 20-24 mg/d). Most of iloperidone-treated patients in any of the study groups 1 to 3 received ILO 10-16 mg/d. Only a small number of patients was included in the highest dosing group ILO 20-24 mg/d, especially for a longer time period of more than six or twelve months (64 and 22 subjects).

Adverse events reported and evaluated for the four different study groups revealed an overall consistent profile for iloperidone. The total adverse event rate for placebo-controlled studies (Study Group 2) was 80.7% for the combined ILO group, lower for the risperidone and placebo group (78.4% and 75.1%) and higher for the haloperidol and ziprasidone group (94.9% and 86.7%). The system organ classes mostly affected throughout study groups were GI-Disorders, Psychiatric Disorders and Nervous System Disorders. Looking again at Study Group 2 for consistency, adverse events with the highest frequency detected in the combined ILO group compared to placebo and the active comparators were: tachycardia (4.2% vs. 0.7% to 2.0%), dry mouth (7.4% vs. 1.2% to 7.3%), dizziness (13.6% vs. 5.1% to 13.3%) and nasal congestion (5.7% vs. 1.7% to 3.3%).

Iloperidone is claimed to depict a favourable profile concerning extrapyramidal symptoms, e.g. Extrapyramidal Disorder, Tremor and Akathisia, since these events were reported in similar frequencies to placebo. Taking into account, that haloperidol was administered in doses of up to 20 mg/d, the relatively high number of patients suffering from EPMS-related adverse events (59.7%) can be partly explained by a high haloperidol dosage. Furthermore, the company did not summarize typical EPMS symptoms to one term “Extrapyramidal Symptoms”.

Cardiac safety is considered of major concern. Since iloperidone bears the risk for QTc prolongation due to its pharmacological action as a pure inhibitor of hERG channels, a thorough QTc study (ILO522 2328) was conducted in mixed schizophrenic and schizoaffective patients.

Mixed schizophrenic and schizoaffective patients were randomized to three ILO dosing groups (8 mg BID, 12 mg BID, 24 mg QD), a positive control group (ziprasidone 80 mg BID) and a negative control group (quetiapine 375 mg BID). A placebo control is missing and quetiapine cannot be considered a negative control, since QTc prolonging effects can also be seen with quetiapine.

As a result, mean QTcF changes from baseline to steady-state during period 1 (absence of metabolic inhibition) were similar for ILO 8 mg BID, ILO 12 mg BID, and ziprasidone 80 mg BID [positive control] and almost twofold higher with ILO 24 mg QD (iloperidone 8 mg BID (8.5 msec), iloperidone 12 mg BID (9.0 msec), iloperidone 24 mg QD (15.4 msec), ziprasidone 80 mg BID (9.6 msec) and quetiapine 375 mg BID (1.3 msec) [negative control].

The addition of paroxetine as metabolic inhibitor during period 2 consequently increased QTc mean changes. Ketoconazole was added as a second inhibitor during period 3 and QTcF mean changes from baseline raised up to iloperidone 8 mg BID (15.7 msec), iloperidone 12 mg BID (19.3 msec), iloperidone 24 mg QD (19.5 msec), ziprasidone 80 mg BID (15.9 msec) and quetiapine 375 mg BID (2.6 msec). A statistically significant relationship between plasma concentration and QTc prolongation was observed for iloperidone in Period 2 and for the metabolite P88 in both Periods 2 and 3; not for ziprasidone or quetiapine.

QTcF interval changes of special concern were detected: QTcF interval increases of ≥30 msec in 31% (44%, and 61%) of patients during period 1 (without inhibitor) receiving ILO 8 mg BID (ILO 12 mg BID, and ILO 24 mg QD) dosing, up to 70% of patients in the 12 mg BID group during period 3. Of

note, since nine consecutive measures were conducted these numbers could relate to patients counted multiple times. Seven patients during period 2 (with CYP2D6 inhibitor) and 3 (with CYP2D6 and CYP3A4 inhibitor in combination) had QTcF interval changes of ≥60 msec (ten patients overall in all secondary analyses) during concomitant medication with a CYP2D6 and CYP3A4 inhibitor. Mean changes in QTc suggest iloperidone and ziprasidone to have an effect on cardiac repolarisation. For iloperidone, this effect results in a considerable number of patients who exceed the threshold of clear clinical concern.

No patient experienced QTc values of 500 msec or more using any correction factor. 22% of patients from the ILO 12 mg BID dosing group had an adverse event belonging to Cardiac Disorders, especially tachycardia. Two patients withdrew for tachycardia during the titration period for iloperidone; both recovered without sequelae. Overall, one serious adverse event was reported related to arrhythmia (supraventricular tachycardia) at iloperidone 8 mg BID with no sequele.

Given the results in the presence of partial and full metabolic inhibition (CYP2D6+CYP3A4), QTcF mean prolongation at iloperidone 12 mg BID as well as 24 mg QD doses are close to substantially increased risk of inducing QTc related reactions (according to *Note For Guidance On The Clinical Evaluation OF QT/QTc Interval Prolongation And Proarrythmic Potential For Non-Antiarrhytmnic Drugs, CHMP/ICH/2/4*).

This study provides evidence that administration of iloperidone at doses of 16-24 mg/day is associated with a substantial prolongation of the QT interval (8.5-15.5 msec). Increasing exposure to iloperidone, P88, or their sum increased QT intervals. Moreover, when considering a worst-case scenario (including CYP2D6 and CYP3A4 metabolic inhibition), a considerable and possibly clinically relevant mean change in QTcF from baseline to steady state at t_{max} was reported at suggested maximal clinical doses [highest in the iloperidone 24 mg QD (19.5+11.9 msec) and iloperidone 12 mg BID (19.3+17.1 msec) groups, followed by the iloperidone 8 mg BID (15.7+14.1 msec) group in Treatment Period 3].

Of note and concern is an observed mean decrease in heart rate during treatment period 2 and 3 (under metabolic inhibition):– 0.9, -3.9, and -4.8 bpm and -1.6, -4.7, and -5.2 bpm for ilo 8 mg BID, 12 mg BID, and 24 mg QD. Decrease in heart rate might contribute to the arrhythmogenic potential of iloperidone since bradycardia is considered a risk factor.

The PK-PD relationship to QTcF supported, according to the applicant, that the QT-prolonging effect plateaued at a c_{max} around 20 ng/mL; exposures slightly lower than those observed at the iloperidone 12 mg BID dose. The applicant stated a plateau-effect for iloperidone, P88, and their sum. However, a plateau could not be detected with P88 and is highly questionable for iloperidone itself due to its mechanistically properties of pure hERG channel blockade.

A further contribution to the QT prolonging effect of iloperidone was assumed by metabolism via CYP2D6. Study 2328 and 3101 examined the most common CYP2D6 polymorphisms. Results from study 2328 indicated that QT prolongation is much more pronounced in patients exhibiting polymorphism of CYP2D6 (CYP2D6*4 and CYP2D6*10, so-called “poor metabolizer”), since these patients had higher plasma concentrations of iloperidone and the active metabolite P88, whereas concentrations of the inactive metabolite P95 decreased. Study 3101 confirmed these results: polymorphisms in CYP2D6 (CYP2D6*4 and CYP2D6*10) were associated with a greater incidence of QTc prolongation in iloperidone-treated patients.

Mutations in the KCNQ1 gene can cause “long QT syndrome”. KCNQ1 finding was part of an exploratory analysis of 58 single nucleotide polymorphism which revealed larger influence on QT prolongation than observed with CYP2D6 polymorphism. Furthermore, a significant interaction between CYP2D6*4 and KCNQ1 (p=0.0015) and CYP2D6*10 and KCNQ1 (p=0.0016) was identified. As a

consequence, patients who carry the polymorphic alleles for both genes experience the longest prolongation of the QTc interval following iloperidone treatment (up to 26 msec).

These results were however not replicated in the Whole Genome Association Study performed within the Study 3101. This discrepancy could not be explained and the risk for patients carrying the polymorphic alleles for both genes is not clearly elucidated. Given the changes observed in the evaluation in the QT study, genotyping for KCNQ1 seem necessary for a safer use of this medicinal product.

QTc data were subsequently reviewed from phase 3 studies: Data from clinical phase 3 studies: QTcF changes for patients in Study Group 2 were dose-related and 3.5, 3.9, and 7.7 msec for ILO 4-8 mg/d, ILO 10-16 mg/d, and ILO 20-24 mg/d from baseline to endpoint. Long-term intake of iloperidone for more than 12 months led to QTcF interval changes of up to 18.5 msec (Study Group 1). Females were more affected than males (4.3% of females vs. 1.3% of males with QTcF interval $\geqslant$450 msec), suggesting a gender difference for QTc abnormalities. This effect is also supposed to be dose-related. Two patients, both males, had QTcF values above 500 msec, which is in contrast to the QTc study results. In the placebo-controlled studies, 23.7% of patients from the combined ILO group and 11.1% placebo-treated patients had a QTcF change of 30 msec and more (ziprasidone group: 31.8%). QTcF changes of more than 60 msec were reported in the risperidone and ziprasidone arm (2.6% and 3.4%) and similar in the combined ILO, placebo and haloperidol group (1.6%, 0.9%, 0.9%).

ECG abnormalities were also found to occur in a higher incidence and dose-related in iloperidone-treated patients. Cardiovascular adverse events were similar in iloperidone- and ziprasidone-treated subjects. However, fatal outcomes of cardiovascular AE were seen to a higher extent in the iloperidone groups. Six deaths occurred in the iloperidone group presumably cardiac-related, of which four may be considered “sudden deaths”. Post-marketing data revealed further deaths related to cardiac interaction.

To minimise the risk for QT prolongation, mandatory genotyping of CYP 2D6 for any patient dosed above 6 mg BID was proposed with subsequent lower dosing recommendations targeting 6-8mg, depending on the CYP2D6 genotype status. However, the variety of circumstances that may lead to increased iloperidone exposure makes the arrythmogenic risk insufficiently reduced. Besides, the dose reduction strategy is not fully supported by study results and sensitivity analyses on short-term efficacy according to which the initially proposed maximum dose of 24mg/d will be needed in a relevant number of patients with schizophrenia.

Serious adverse events and deaths

Overall, 16 deaths were recorded under iloperidone treatment during all studies. All deaths occurring on-study or post-study have been judged as not related to iloperidone as study medication by the investigators except for one death in Study 3002 (patient 056-1012, reported as sudden death). Seven of the deaths, which occurred under iloperidone treatment, are suspected to be cardiac-related. According to the information provided by the company, four of the cardiac-related deaths may be considered “sudden deaths”. Narratives of these patients do not exclude a relationship to iloperidone treatment and its cardiac effect.

A formal investigation of suicide-related adverse events and suicidality in general according to the “Draft Guideline on Clinical Investigation of Medicinal Products in the Treatment of Schizophrenia (CHMP/40072/2010) has been requested and provided in the response.

Four completed suicides were reported on iloperidone vs none on placebo and only one on comparator. Narratives from two additional completed suicides in post-marketing experience during the post-marketing experience period January 2010 (market launch) - May 2012 in the US were not evaluable due to scarce and inadequate information.

Available data do not allow for a comprehensive conclusion, given the relatively limited amount of data. A larger suicide rate was thus reported for iloperidone from clinical trials compared to active comparators (and placebo) while the exposure-adjusted suicide rate based on prescription data referred to by the Applicant, and in comparison with data from the literature, does not confirm an increased suicide rate for ILO.

However, given the increased clinical risk for lack of efficacy at lower iloperidone dosing regiments and the need for titration and complementary medication during this period, the potential increased risk for suicidality indicated and suicidal ideation cannot be excluded.

Laboratory evaluation during the clinical study program does not raise particular new concerns not already known from other atypical antipsychotics. Hepatic analytes like AST and ALT increased for iloperidone in Study Group 1 population. However, these findings could not be seen in the placebo-controlled Study Group 2. Of note, more than or equal to fivefold elevation above the upper limit of normal (ULN) for alanine aminotransferase (ALT) was seen in iloperidone-treated patients compared to placebo. Prolactin concentrations were also measured and as already mentioned revealed a favourable profile for iloperidone, most similar to ziprasidone.

Iloperidone demonstrated an effect on various vital signs investigated during clinical studies: pulse rate was elevated in 29.2% of ILO-treated patients versus 6.7% of placebo-treated patients (Study Group 2) assuming to be less pronounced during long-term treatment. Pulse rate increases in a high number of iloperidone-treated patients is concerning against the background of cardiac effects of iloperidone. Its alpha adrenergic properties led to a significant decrease of blood pressure compared to placebo and other active comparators. Acute orthostatic hypotension happened in 17.8% of patients in the ILO combined group vs. 7.6% in the placebo group (Study Group 1). The effect of iloperidone on weight increase appears to be in line with those known from other antipsychotic substances and to be more pronounced during the first six weeks of treatment.

Age evaluation did not account for any unexpected safety findings. The same is true for gender analysis. Nevertheless, females are exposed 50% more to iloperidone compared to male. Although no clinically significant differences concerning adverse events could be determined, there could be an increased risk for females for cardiovascular AEs since QTc prolongation was proven to increase with plasma concentrations of iloperidone. No firm conclusion regarding the impact of gender on the pharmacokinetics of iloperidone can be drawn from the population pharmacokinetic analysis.

Iloperidone use in mild to moderate hepatically impaired subjects was evaluated in study ILO522 0103, revealing subjects with hepatic impairment to have higher exposure to P88 compared to healthy control subjects but nearly the same exposure to iloperidone. Furthermore, a single 2-mg-dose is not considered to reveal possible safety concerns, since doses will be 12-24mg per day in the real setting. A clear distinction between mild and moderate hepatic impairment is missing in the study report. Study ILO522 0103 is therefore considered to have several shortcomings regarding the dose and clear presentation of the results in mild and moderate hepatic impairment is not provided.

Iloperidone is currently marketed in the United States, Argentina and Israel. Post-marketing data presumably derive from 12,000 treated patients in the United States over a period of almost three years. Review of post-marketing data for iloperidone identified 20 cases of deaths. In most of the cases presented, patient data are sparse. “Sudden death” could be assumed for eight of these death cases. There seems to be no relationship to sex, age, or administered doses.

Conclusions on the clinical safety

The main safety concern relates to the cardiac safety profile of iloperidone.

To minimise the risk for QT prolongation, mandatory genotyping of CYP 2D6 for any patient dosed above 6 mg BID was proposed with subsequent lower dosing recommendations targeting 6-8mg, depending on the CYP2D6 genotype status. However, the variety of circumstances that may lead to increased iloperidone exposure makes the arrythmogenic risk insufficiently reduced.

Given the results of the non-clinical studies, QT study and data from use of the product showing a clear arrhythmogenic potential, the CHMP considered that the cardiac risks associated with the use of iloperidone is not considered manageable by risk minimisation measures.

2.7. Pharmacovigilance

Detailed description of the pharmacovigilance system and Risk Management Plan

The CHMP, having considered the data submitted in the application was of the opinion that it was not appropriate to conclude on pharmacovigilance and risk minimisation activities at this time.

3. Benefit-Risk Balance

Benefits

Beneficial effects

Iloperidone short-term efficacy was evaluated and demonstrated in four pivotal trials of 4 to 6 week duration (3101, 3000, 3004, 3005), including a total of 2081 schizophrenic patients and using iloperidone doses of 4 to 24 mg/d. Primary efficacy parameter was reduction of PANSS and BSPRS, respectively, compared to baseline.

Iloperidone 24 mg/d was compared to placebo in the short-term study 3101 which was the only pivotal short-term study exclusively conducted in schizophrenic patients. The PANSS reduction with iloperidone 24 mg differed statistically significant from placebo at week 4 (-12.0 vs. -7.1) but the effect appears modest.

Other short-term studies included a mixed population of patients with schizophrenia and schizoaffective disorder. Post hoc analyses on schizophrenic patients from pivotal studies 3000, 3004 and 3005, together with phase II study B202, as well as responder analyses support an efficacious dose range of iloperidone of 12-24 mg/d for short-term treatment of schizophrenia, although data are heterogeneous.

Uncertainty in the knowledge about the beneficial effects.

All short-term placebo-controlled pivotal studies included an active comparator arm. Whilst these studies were not powered to formally compare iloperidone and the active comparators, it is noted that iloperidone appeared numerically less efficacious than risperidone, however, comparable to haloperidol and ziprasidone.

The titration period for iloperidone is 4 to 7 days (4 days to reach 12mg/d and 7 days to reach the maximum dose of 24mg/d), requiring up to 5 additional days to achieve steady-state exposures, which is a disadvantage.

The Applicant has made proposals to minimize the QT risk of the drug, amongst others recommending a target dose of 6 - 8mg twice daily (12-16mg/d) according to CYP2D6 Genotype status and for maintenance therapy a dose of 6 - 8mg twice daily (12-16mg/d). This strategy cannot fully be

supported in regard to short-term efficacy, as the study results and sensitivity analyses might suggest that the maximum dose of 24mg/d will be needed in a relevant part of patients.

Long-term efficacy of iloperidone was evaluated in a total of 1446 schizophrenic patients in three double-blind, randomised, haloperidol-controlled studies (3001, 3002, 3003). Those studies were identical in design and results were analyzed from a pre-defined pooled analysis. Iloperidone 4-16 mg/d was not non-inferior to haloperidol with a relapse hazard ratio of 1.340 and a 95%-CI of (1.001, 1.795). The upper bound of the 95%-CI was above the predefined non-inferiority margin of 1.676. The predefined non-inferiority margin was also considered too wide and was transformed from a margin of 15 percentage points for relapse (assuming a proportion of relapsers of 30% in the haloperidol group). The definition of response was not clinically appropriate and drop out in the long-term studies was high. Furthermore, the predefined primary analysis was not based on randomised groups. The lack of randomisation of patients at the start of the time-to-relapse period of the study might have introduced bias due to different selection mechanisms during the acute treatment phase.

Post-hoc analyses on selected subgroups of responders using definition of responders recommended by the CHMP (>30% change in PANSS) showed that iloperidone would be non-inferior to haloperidol with an upper bound of the CI smaller than the pre-defined threshold (1.363 vs. 1.676). This suggests that if the absolute non-inferiority margin was 8%, iloperidone would have been shown to be non-inferior to haloperidol when using the new responder definition. However, the sensitivity analyses presented have major methodological shortcomings. They are not based on randomised groups and all additional analyses were performed post-hoc. Drop out in the initial double-blind phase until day 42 was 19% (iloperidone) vs. 26% (haloperidol). Drop out due to unsatisfactory therapeutic effect was similar for iloperidone and haloperidol (8% and 7%), however, bias due to selection cannot be excluded as randomisation prior to entry in the subsequent DB double-blind phase was lacking. For the presented post-hoc analyses type I error is not controlled, as would be normally required for demonstration of long-tern efficacy. For the aforementioned reasons, long-term efficacy has not been sufficiently demonstrated for iloperidone.

Risks

Unfavourable effects

The main safety concern relates to the cardiac safety profile of iloperidone.

As iloperidone is a pure agonist of hERG channels, a thorough QT study (study 2328) was performed to investigate its effect on QT interval in humans. In this study, iloperidone at doses of 16-24 mg/day is associated with a substantial prolongation of the QT interval (8.5-15.5 msec). The clinical consequences of QT prolongation might be cardiac arrhythmia, potentially culminating in Torsade de Pointes and sudden deaths.

Iloperidone interacts with CYP 2D6 and CYP 3A4 inhibitors. When iloperidone 16-24 mg/day was co-administered with CYP2D6 and CYP3A4 inhibitors (paroxetine and ketoconazole) in study 2328, plasma concentrations for iloperidone and its active P88 metabolite are increased and lead to even greater prolongation of the QT interval (16-19.5 msec). Under those full metabolic inhibition conditions, 52% of patients in the 8 mg BID group had a QTcF interval change of ≥30 msec and seven patients had QTcF interval changes of ≥60 msec at tmax.

Study 2328 and 3101 examined the most common CYP2D6 polymorphisms. Results from study 2328 indicated that QT prolongation is much more pronounced in the patients with genetic polymorphisms of CYP 2D6 (CYP2D6*4 and CYP2D6*10), so called poor metabolisers (PMs). PMs were reported to have a

57% increase in iloperidone exposure, about 95% increase in the active metabolite P88, which also increases QT interval, and about 80% decrease in the inactive metabolite P95, resulting in a 152% higher exposure to the active moieties from a given dose of iloperidone compared to extensive metabolizers (EM).

Mutations in the KCNQ1 gene can cause “long QT syndrome”. KCNQ1 finding was part of an exploratory analysis of 58 single nucleotide polymorphism which identified a larger influence on QT prolongation than observed with CYPOD2D6 polymorphism, and a significant interaction between CYP2D6*4 and KCNQ1 and CYP2D6*10 and KCNQ1. These results were however not replicated in the Whole Genome Association Study performed within the Study 3101. This discrepancy could not be explained and the risk for patients carrying the polymorphic alleles for both genes is not clearly elucidated.

With respect to bradycardia, the QT study 2328 revealed a significant decrease in heart rate following CYP2D6 and/or CYP3A4 inhibitors administration of up to - 0.9, -3.9, and -4.8 (paroxetine only) bpm and -1.6, -4.7, and -5.2 bpm (paroxetine and ketoconazole) for iloperidone 8 mg BID, 12 mg BID, and 24 mg QD. Decreases in heart rate have been also observed in phase III studies, providing additional evidence for the arrhythmogenic potential of iloperidone.

In the overall clinical programme, six out of 16 deaths during iloperidone treatment are suspected to be cardiac-related. Another fatality was referred to as a “probable pyloric obstruction and death from pylorus occlusion”. Since this patient received cisapride as co-medication, this death is also regarded as possibly cardiac-related consequent to a drug-drug interaction. Four of these deaths are considered “Sudden Deaths”. Review of 3-years postmarketing data for iloperidone from the US identified 20 death cases. Eight of these deaths were originally presented by the applicant as “Sudden Deaths” but 3 were subsequently reclassified as non-Sudden deaths cases. Four of these eight cases had one or more risk factors.

To minimise the risk for QT prolongation, mandatory genotyping of CYP 2D6 for any patient dosed above 6 mg BID was proposed with subsequent lower dosing recommendations targeting 6-8mg, depending on the CYP2D6 genotype status. However, the variety of circumstances that may lead to increased iloperidone exposure makes the arrythmogenic risk insufficiently reduced.

Given the results of the non-clinical studies, QT study and data from use of the product showing a clear arrhythmogenic potential, the CHMP considered that the cardiac risks associated with the use of iloperidone is not considered manageable by risk minimisation measures.

Uncertainty in the knowledge about the unfavourable effects

Studies in special populations do not fully exclude special conditions to interfere with iloperidone treatment. The hepatic impairment study and the renal impairment study were conducted with low, single doses (up to 3mg), which do not reflect the target doses and additional studies would be necessary to adequately document the safe and effective use of iloperidone in those patients.

Age evaluation did not account for any unexpected safety findings. The same is true for gender analysis. Nevertheless, females are exposed 50% more to iloperidone compared to male. Although no clinically significant differences concerning adverse events could be determined, there could be an increased risk for females for cardiovascular AEs since QTc prolongation was proven to increase with plasma concentrations of iloperidone. No firm conclusion regarding the impact of gender on the pharmacokinetics of iloperidone can be drawn from the population pharmacokinetic analysis.

Females subjects seem to have an approximate 50% higher exposure (weight corrected) to iloperidone than males. Higher iloperidone exposure may support a higher risk for QT prolongation in females compared to men. Based on the population pharmacokinetic analysis, a firm conclusion cannot be drawn regarding the gender effect on the PK of iloperidone. Further investigations would be needed to better inform the potential gender differences with regard to QTcF-prolongation for iloperidone.

Regarding drug-drug interactions, a number of interactions due to inhibition of iloperidone's metabolism is considered possible, mainly via CYP2D6 and CYP3A4 inhibition. The patient population, for which the use of iloperidone is intended, often receives polymedication. The interaction of major concern in patients of unknown CYP2D6 metaboliser status is the administration of a strong CYP3A4 inhibitor. While the thorough QT study is representative for this situation, the QT prolongation by iloperidone in patients with KCNQ1 mutations is however still unclear.

Assessment of the suicidality analysis submitted in the response concluded that available data do not allow for a comprehensive conclusion, given the relatively limited amount of data. A larger suicide rate was thus reported for iloperidone from clinical trials compared to active comparators (and placebo) while the exposure-adjusted suicide rate based on prescription data referred to by the Applicant, and in comparison with data from the literature, does not confirm an increased suicide rate for iloperidone. However, given the increased clinical risk for lack of efficacy at lower iloperidone dosing regiments and the need for titration and complementary medication during this period, the potential increased risk for suicidality indicated and suicidal ideation cannot be excluded.

Iloperidone is claimed to exert a favourable profile on extrapyramidal symptoms (especially Akathisia), compared to other products in the class. However, this was fully confirmed in the clinical programme.

Benefit-risk balance

Importance of favourable and unfavourable effects

Additional pharmacological treatment options are needed in schizophrenia. Moderate short-term efficacy of iloperidone has been demonstrated, and whilst this has not been fully confirmed in the clinical programme, iloperidone is claimed to exert a favourable profile on extrapyramidal symptoms (especially Akathisia), and prolactin elevation compared to other products in the class.

However, long-term efficacy has not been sufficiently demonstrated and this should be done prior to approval. In addition, whilst short-term studies were not powered to formally compare iloperidone and the active comparators, iloperidone appeared numerically less efficacious than risperidone, however, comparable to haloperidol and ziprasidone. The long titration period for iloperidone also is considered a disadvantage.

The cardiac safety profile of iloperidone is a major concern. Given the results of the non-clinical studies, QT study and data from use of the product showing a clear arrhythmogenic potential, the CHMP considered that the cardiac risks associated with the use of iloperidone is not considered manageable by risk minimisation measures.

Benefit-risk balance

The CHMP considered the benefit-risk balance for iloperidone treatment of schizophrenia in adults to be negative.

Discussion on the benefit-risk balance

Pronounced arrhythmogenic and torsadogenic potential iloperidone is indicated by the totality of non-clinical and clinical data. This risk is not considered manageable by risk minimisation measures. In addition, the dose reduction strategy proposed by the Applicant to reduce cardiotoxity is not sufficiently supported by data. The study results and sensitivity analyses on short-term efficacy suggest that the initially proposed maximum dose of 24mg/d will be needed in a relevant number of patients with schizophrenia. Long-term efficacy has not been sufficiently demonstrated. Short-term efficacy is modest, and the delayed onset of effect of iloperidone is a disadvantage. Overall, the CHMP could not identify a target population or a treatment setting where the modest benefits of iloperidone could outweight the major safety concerns.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy for Fanaptum in the treatment of schizophrenia, the CHMP considers by consensus that

the safety and efficacy of the above mentioned medicinal product is not sufficiently demonstrated,

and, therefore recommends the refusal of the granting of the Marketing Authorisation for the above mentioned medicinal product. The CHMP considers that:

- The totality of non-clinical and clinical data for iloperidone indicates a pronounced arrhythmogenic and torsadogenic potential. This risk is not considered manageable by risk minimisation measures. In addition, the dose reduction strategy proposed by the Applicant to reduce cardiotoxity is not sufficiently supported by data. The study results and sensitivity analyses on short-term efficacy suggest that the initially proposed maximum dose of 24mg/d will be needed in a relevant number of patients with schizophrenia.

- Long-term efficacy has not been sufficiently demonstrated.

- Short-term efficacy is modest, and the delayed onset of effect of iloperidone is a disadvantage. Overall, the CHMP could not identify a target population or a treatment setting where the modest benefits of iloperidone could outweight the major safety concerns.

Due to the aforementioned concerns a satisfactory summary of product characteristics, labelling, package leaflet, pharmacovigilance system, risk management plan and follow-up measures to address other concerns as outlined in the list of outstanding issues cannot be agreed at this stage.

Furthermore, the CHMP, in light of the negative recommendation, is of the opinion that it is not appropriate to conclude on the new active substance status at this time.