Annex I

Scientific conclusions and grounds for refusal presented by the European Medicines Agency

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Overall summary of the scientific evaluation of Fanaptum

- **Quality**

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

- **Non-clinical**

Iloperidone and the metabolite P88 shows relatively high affinity for hERG channel (IC50 of 12.4 and 24.1 ng/mL). This indicates that Iloperidone could cause QT prolongation. Action potential prolongation was observed in ventricular dog Purkinje fibres, confirming the pro-arrhythmogenic potential of Iloperidone. No QT prolongation was observed in the in vivo dog studies. However, the exposure in the dog studies appears to be lower than in the clinical setting, and therefore the absence of any QT prolongation in the in vivo dog studies is not considered to alleviate the concerns raised based on the in vitro studies.

The arrhythmogenicity of Iloperidone is mechanistically related to its selective inhibition of cardiac potassium channels leading to delayed repolarization which is seen in the characteristic action potential prolongations in ventricular dog Purkinje fibres. Iloperidone lacks any significant affinity for cardiac sodium and/or calcium channels at therapeutic plasma concentrations. Thus, mechanisms that could potentially mitigate the prominent pro-arrhythmogenic potential of iloperidone are not present.

The overall nonclinical safety pharmacology data point to a risk of QT prolongation (hERG blockade, APD prolongation in dog Purkinje fibres).

- **Efficacy**

The short-term efficacy of Fanaptum in patients with an acute episode of schizophrenia has been mainly characterised in five placebo-controlled studies. Of those, three – B202, 3000, and 3005 – failed to show superiority over placebo according to their pre-specified primary endpoints and analysis plans, and two – 3004 and 3101 – met their pre-specified criteria for superiority over placebo. However, Study 3004 also included patients with schizoaffective disorder and efficacy was not demonstrated in the schizophrenia subgroup. Thus, Study 3101 was the only positive short-term study exclusively conducted in schizophrenia patients. In this study, the PANSS reduction with Iloperidone 24 mg differed in a statistically significant manner from placebo at Week 4 but the magnitude of the effect was modest with a reduction of approximately 5 points on the PANNS-T scale compared to placebo.

The efficacy of daily doses lower than 24 mg was insufficiently characterised. Doses as low as 4-8 mg/day appeared effective in one study (3004), and in some studies doses of 12 mg/day (3000), 10-16 mg/day (3004) or 12-16 mg/day (3005) likewise showed superiority to placebo. However, no correction for multiplicity was performed when evaluating individual doses. Thus, efficacy has not been convincingly established for 12 mg/day dose. PK-PD analyses presented were fundamentally flawed in that placebo patients were included with an assigned value of zero – impacting the results of the analysis. In conclusion, there was no robust support for statements concerning dose-response relationship below 24 mg/day (the dose used in study 3101).

An active comparator was included in studies 3000 (Haloperidol), 3004 and 3005 (Risperidone), and 3101 (Ziprasidone). Although comparative efficacy was not the primary objective of those studies, the magnitude of effect of Fanaptum appeared similar to Ziprasidone but compared negatively with

Haloperidol and Risperidone. The Applicant argued that the apparent difference between Fanaptum and risperidone could be partially due to a greater number of patients on Fanaptum discontinuing early due to lack of efficacy during titration. However, post-hoc analyses presented in support of this argument were based on patients completing at least 2 weeks of treatment, which is a different population from that originally assigned to treatment. Furthermore, risperidone was still associated with a numerically superior effect estimate - even for patients treated for >2 weeks.

Compared to other antipsychotics, Fanaptum has a late onset of action. Several approaches to various data sets support the notion that full efficacy of Fanaptum is not achieved before Week 3. For instance, in Study 3101 where full effect vs placebo would correspond to a reduction of 5 PANSS-T points, it is remarkable that the difference at Week 1 was already 2.4 for ziprasidone, whereas it was 0.1 for Fanaptum. Similarly, at Week 2 it was 4.2 for ziprasidone i.e. almost full efficacy, whereas the difference was still only 2.8 for Fanaptum. Late onset of action is regarded as a considerable drawback.

Continued, long-term efficacy after stabilisation with Fanaptum has been studied and demonstrated in Study 2301, in which patients continuing on Fanaptum had a significantly lower rate of relapses or impending relapses compared to patients switched to placebo. However, as the randomised withdrawal study by design has to include the responders only i.e., the population is enriched, the magnitude of the effect can only be derived from the short term studies. Additional data has been provided from the open-label Study US01–comparing two ways of switching to Fanaptum from another treatment, gradual (over two weeks) or immediate. However, this study – with an open label design and lacking of a group of patients randomised to a treatment other than Fanaptum or to placebo - was not designed to establish efficacy in patients switching from another treatment.

The indirect comparison for efficacy proposed by the Applicant does not fulfil the methodological standards of systematic reviews (for instance, comprehensive search strategy, transparent and replicable inclusion criteria), and this limits the reliability of the conclusions that can be drawn from it.

In conclusion, Iloperidone has a modest efficacy. In addition, it has shown a delayed onset of action, which is a significant concern in the treatment of acute exacerbation of schizophrenia.

- **Safety**

The main safety issue with Iloperidone is that it causes QTc prolongation with the subsequent risks of arrhythmia and sudden death.

Iloperidone has a high affinity to the hERG channels and causes QTc exposure-dependent prolongation. In the thorough QTc study (Study CILO522A2328), the mean change in QTcF from baseline to steady state at Tmax was approximately 9 msec in the 8 mg and 12 mg BID groups and was 15.4 msec in the group receiving Iloperidone 24 mg q.d. compared to 1.3 msec in the group receiving quetiapine (negative control).

In reviewing the results of the thorough QTc study, out of 94 patients exposed to Iloperidone at different doses without metabolic inhibition in the Secondary QTc population 43 and 2 patients respectively developed a prolongation of the QTcF of more than 30 and 60 msec.

In the clinical trial programme, 4.5% of the patients treated with iloperidone regardless of dose (4-24 mg/day) had an increase more than 60 msec at some time point.

There were 6 cases of sudden deaths or deaths due to cardiac AE in the clinical trials. As 4423 patients were exposed to Iloperidone, this accounts for 0.14% of all treated patients. Very little detailed information is available from the post-marketing setting. There were 33 deaths of which 3 patients died during sleep, 6 were sudden deaths, and 6 cases were of cardiac origin. At least one fatal case could

possibly have been preceded by ventricular arrhythmia and Torsades de Pointes. In addition, there is at least one literature case report of arrhythmia. Unfortunately, the CYP2D6 genotype was not known in the patients that died during the clinical studies or post-marketing.

Furthermore, as the metabolism of iloperidone relies heavily on CYP3A4 and CYP2D6, this creates the potential of increased exposure to the drug as a consequence of drug-drug interactions and genetic polymorphisms. Acknowledging the relationship between QTc prolongation (and the connected risks) and exposure, the Applicant proposed for this re-examination a contraindication in CYP2D6 poor metabolisers or in those patients with unknown CYP2D6 metaboliser status, and for concomitant use with drugs that are known strong CYP2D6 or CYP3A4 inhibitors.

However, the metabolism of Iloperidone is still of concern in relation to its exposure-dependent risks. It is currently unknown if Iloperidone can be safely administered with weak and/or moderate inhibitors of CYP2D6 and/or CYP3A4 given the likely variability of the efficiency of minor metabolic pathways. This means that, from a precautionary approach, patients could not safely be concomitantly treated with a large number of other medicines.

In conclusion, Iloperidone has a substantial arrhythmogenic potential, which becomes obvious if all available non-clinical and clinical data (including the thorough QTc study, the overall clinical program and also the cases of cardiac-related/sudden unexplained death in clinical trials and post-marketing) are taken into account.

In consideration of the complex causal chain linking the exposure to Iloperidone to events such as Torsade de Pointes, including unknown and stochastic elements and elements subject to an unpredictable variability, it is considered that the risk minimization measures proposed would not adequately address in clinical practice the risk identified. For example, the proposal to perform ECGs at the estimated Tmax could miss the actual Tmax due to intrinsic or extrinsic factors, leading to an underestimation of the QTcF prolongation.

In addition, whether the correct implementation of the complete set of measures would be feasible in all clinical settings is questionable due to practical reasons (for example the availability of suitably trained cardiologists), as also mentioned by the Experts in the ad-hoc meeting.

Iloperidone is associated with extrapyramidal effects, but to a modest degree. In particular, Akathisia was reported at lower rates in patients treated with Iloperidone than in patients treated with the active comparators in the active-controlled trials submitted, where the comparators were antipsychotics with an acknowledged degree of propensity to cause Akathisia at the doses studied.

As mentioned for the one related to Efficacy, the indirect comparison for Akathisia proposed by the Applicant does not fulfil the methodological standards of systematic reviews (for instance, comprehensive search strategy, transparent and replicable inclusion criteria), and this limits the reliability of the conclusions that can be drawn from it.

Iloperidone is also associated with a clinically significant body weight increase.

In summary, the safety of Iloperidone has not been sufficiently demonstrated.

Grounds for refusal

Whereas

- Considering all available non-clinical and clinical data (including the thorough QTc study, the overall clinical program and the cases of cardiac-related/sudden unexplained death in clinical trials and post-marketing), Iloperidone has a substantial and exposure-dependent arrhythmogenic potential. It is not considered that the risk minimization measures proposed

would appropriately address the risk identified in this specific case. Hence, the safety of Iloperidone has not been sufficiently demonstrated.

- Furthermore, Iloperidone has a modest efficacy. In addition, it has shown a delayed onset of action, which is a significant concern in the treatment of acute exacerbation of schizophrenia. Therefore, and taking into account the overall safety and efficacy profile of Iloperidone a patient population cannot be identified where the benefit of treatment is considered to outweigh the major safety concerns.

Based on the above, the risk-benefit balance of Iloperidone is considered negative.

The CHMP is of the opinion that pursuant to Article 12 of Regulation (EC) No 726/2004, the safety of the above mentioned medicinal product is not properly or sufficiently demonstrated.

Therefore, the CHMP has recommended the refusal of the granting of the marketing authorisation for Fanaptum.