Annex II

Scientific conclusions and grounds for positive opinion presented by the European Medicines Agency

Scientific conclusions

Overall summary of the scientific evaluation of Methylphenidate Sandoz and associated names (see Annex I)

Methylphenidate Sandoz which contains the active substance methylphenidate hydrochloride is an osmotic controlled prolonged release film coated tablet with a bi-layer core. The product is a biphasic modified release formulation, with an immediate release (IR) phase and a prolonged-release (PR) phase.

Methylphenidate Sandoz (18 mg, 36 mg and 54 mg) is indicated in the treatment of Attention Deficit/Hyperactivity Disorder (ADHD) in children aged between 6 and 18 years old once daily in the morning and can be taken with or without food. The application for Methylphenidate Sandoz is therefore based on bioequivalence studies between the applied and the reference product.

The repeat-use MRP marketing authorisation application presented for the medicinal product Methylphenidate Sandoz 18mg, 36mg, 54mg tablets is a generic application in accordance with the Article 10.1 of the Directive 2001/83/EC. The application for Methylphenidate Sandoz is therefore based on bioequivalence studies between the applied and the reference product.

During the repeat-use MRP, Germany and the Netherlands expressed the opinion that bioequivalence under fed conditions using the partial metrics (i.e. Concentration maximal (0-2h) ($C_{max(0-2h)}$), Area Under the Curve$_{(0-2h)}$ ($AUC_{(0-2h)}$), $C_{max(2-24h)}$, $AUC_{(2-24h)}$) had not been shown between the applied and the reference product. The fed study failed to fulfil the standard acceptance criteria for bioequivalence for the immediate-release phase ($AUC_{(0-2h)}$ and $C_{max(0-2h)}$). The use of partial metrics under fed condition was considered necessary as the reference product can also be taken with food. Therefore bioequivalence under fed conditions for the two phases of absorption (IR and PR) should be demonstrated. Furthermore, the extrapolation of the fed study conducted with the highest strength 54mg to the lower strengths was not considered acceptable.

The repeat-use MRP was closed on day 210, with most of the CMS agreeing with the conclusions of the RMS's assessment report except Germany and the Netherlands which raised a potential serious risk to public health (PSRPH). A referral was thus triggered at the CMD(h). The major concern raised by Germany and the Netherlands could not be solved during the CMD(h) referral, and the issue was therefore referred to the CHMP.

According to the Questions & Answers: Positions on specific questions addressed to the pharmacokinetics working party (EMA/618604/2008 Rev. 7. 13 February 2013) for a generic biphasic modified release formulation, equivalence with the reference product needs to be shown for both extent and rate of absorption (reflecting AUC and C_{max} for conventional bioequivalence criteria), separately for both the immediate release and extended release phases:

- For the first phase, the assessment of equivalence should be based on the truncated AUC from t=0 until the cut-off time describing the immediate release dose fraction, and on C_{max} during the first phase.
- For the second phase, the assessment of equivalence should be based on the AUC from the cut-off time until the end of observation period, and on C_{max} during the second phase.

These considerations are in principle valid for studies in fed state and in fasting state. If no significantly different pharmacokinetic profile between fasting and fed state is expected then the cut-off time point should be identical.

The first pharmacokinetic studies were performed by the applicant/MAH in 2009-2010 and submitted in the first DCP starting in January 2011. The current repeat use procedure started in April 2012, two months after the EMA Question & Answer Position Paper (EMA/618604/2008 Rev. 4) concerning biphasic formulations was published. Because the pharmacokinetic studies were performed in 2009-2010 the Q&A Position Paper was not taken into consideration by the applicant/MAH.

Pharmacokinetic data

In support of the application, the applicant/MAH performed three single dose studies under fasting conditions with the 18, 36 and 54 mg tablets and one single dose study under fed conditions with the 54 mg tablet. The applicant/MAH requests extrapolation of the results from the fed study with 54 mg tablet to the lower strengths.

The studies under fed and fasting conditions demonstrated bioequivalence between test and reference product using the entire dose interval ($AUC_{(0-24h)}$ and $C_{max(0-24h)}$). The 90% CI for these measures were within the acceptance interval of 80%-125%. The studies demonstrated bioequivalence between test and reference product according to the guideline requirements for a modified release dosage form (*Guideline on the investigation of bioequivalence, 2010 CPMP/EWP/QWP/1401/98 Rev. 1* and *Note for Guidance on Modified Release Oral and Transdermal Dosage Forms, 1999 EMA/CPMP/EWP/280/96 Corr*)* in force at time of study conduct (2009 – 2010).

In a post-hoc analysis, the applicant/MAH further provided results for partial metrics (AUC and C_{max}) for the immediate release phase and the extended release phase within 0-2 hours and 2-24 hours. The results showed that bioequivalence was demonstrated for the studies under fasted conditions between Methylphenidate Sandoz (18mg, 36mg, 54mg) and the reference product for the immediate and prolonged release phase. However, the pharmacokinetics (PK) parameters for the immediate release phase ($C_{max(0-2h)}$, $AUC_{(0-2h)}$) for the fed study were not within the conventional criteria of 80%-125%. The PK parameters for the fed study for the immediate release phase were the following: $C_{max(0-2h)}$ = 74.8 -142.7 and $AUC_{(0-2h)}$ = 60.0 – 155.6 (90% CI).

The applicant/MAH claimed that this is primarily attributed to the high intra-subject variability (66.5% for $C_{max(0-2h)}$, 110.1% for $AUC_{(0-2h)}$) observed in this early phase as the point estimators $C_{max(0-2h)}$ and $AUC_{(0-2h)}$ are very close to 100% indicating that with an adequate sample size bioequivalence could have been shown also for these two parameters.

To support the claim that the high variability seen in the fed study is attributed to physiological conditions after intake of a high fat meal and not differences between the test and reference formulations, a discussion on literature data and the results obtained in the fed study is provided.

Lee *et al.* 2003 investigated the pharmacokinetics of Ritalin LA 40 mg capsule (Methylphenidate hydrochloride also consisting of an IR and ER component) under fasted conditions and after administration of a high fat breakfast. They observed that initial methylphenidate profiles were more variable between the subjects in the fed state than in the fasted state.

Regarding the results obtained in the fed study (2009-18-PRT-2), it was shown that when compared to the fasting study several subjects did not have a biphasic profile but a continuous profile without an early maximum, whereby methylphenidate concentrations slowly increase after an erratic lag time. Two types of profiles were seen. The first profile was a biphasic profile (“target profile” of the reference product Concerta) with an early maximum followed by a decrease or an approximated plateau in the plasma concentrations. The second profile was a continuous profile without an early maximum, whereby methylphenidate concentrations slowly increase after an erratic lag time.

The applicant/MAH claimed that the administration of a biphasic methylphenidate modified release formulation with a high fat meal has a major impact on the gastric emptying and transit time, and therefore, can lead to different shapes in the pharmacokinetic profiles in the early absorption phase.

Although the immediate-release part of the dosage form also quickly dissolves, this occurs in the middle of the chyme. Thus, the dissolved drug is trapped by the high-fat meal in the stomach and cannot easily bypass the stomach contents. Consequently, the dissolved drug from the immediate-release portion of the dosage form only reaches the intestine with delay. In consequence, the sustained process of absorption of the immediate release fraction appears to overlap with the absorption of the prolonged release fraction of the biphasic formulation.

A clear cut-off between the immediate and extended release fraction as required by the Q&A position paper is not feasible under these conditions.

The applicant/MAH further provided a re-evaluation of the data from the fed study based on the different types of plasma profiles observed in this study. The study evaluated the subjects which showed the characteristic biphasic profile of methylphenidate osmotic release formulation during the initial phase for both test and reference (n=8), and excluded subjects showing a continuous profile for at least one of the treatments.

The results showed that by identifying true biphasic profiles for the early absorption phase, bioequivalence for both the AUC and C_{max} during the initial phase between both investigational products is proven. This is also due to the fact that the intra-individual variability decreased (19% instead of 110% for AUC, and 12% instead of 67% for C_{max}) by taking into account only those subjects who exhibit a distinct peak for the initial phase under high fat fed conditions.

The CHMP is of the opinion that the applicant/MAH provided sufficient evidence to prove that the variability seen in the fed study (0-2 hours) is not related to differences between the test and reference product, but is related to a food-induced effect, which delays the absorption of the active substance from the immediate release layer.

Pharmaceutical data

Methylphenidate Sandoz's formulation is designed with an outer coating containing the immediate-release part surrounding the prolonged-release core (osmotic controlled). In comparison to the originator product, the test product contains similar excipients in the same amounts in the outer drug coat. The dissolution is rapid for the outer coating and similar between the test and reference product in various media in the pH range 1 to 6.8 as well as in FeSSIF (Fed state simulated intestinal fluid) and FeSSGF (Fed state simulated gastric fluid).

The additional in vitro dissolution profiles of test and reference product without the immediate release coating demonstrate that a lag time is seen for the prolonged release part and that the active substance in the immediate layer is released fast and independent from the prolonged release part. All in vivo and in vitro results indicate that the prolonged release phase (osmotic controlled) is unaffected by food intake. Bioequivalence has been demonstrated for the prolonged release phase (2-24h) for AUC and Cmax under fed and fasting condition.

Based on the discussion above, it is considered reasonable to look at the immediate release phase separately, and fasting conditions is considered more sensitive in relation to detect difference between test and reference for a highly soluble immediate release formulation in order to provide proof of bioequivalence.

Waiver of studies under fed conditions for the 18 mg and 36 mg strengths

The bioequivalence under fed conditions has only been studied in the 54 mg strength. The fed study conducted with the highest strength 54mg was extrapolated to the lower strengths (18 and 36 mg). The waiver of studies under fed conditions for the lower strengths are considered justified for the following reasons:

- all strengths have the same qualitative composition
- all strengths are manufactured by the same manufacturer and process
- all strengths shows comparable dissolution profiles in various media in the pH range 1 to 6.8, in FeSSIF and FeSSGF
- methylphenidate exhibits linear kinetics among all strengths
- The outer drug coat is proportional in composition among all strengths and the ratio between the amount of the semipermeable membrane and the surface area are comparable amongst all strengths for the applied product. These ratios are considered as key element responsible for the controlled release of the drug from the tablet core.

In addition, the draft guideline on pharmacokinetic and clinical evaluation of modified release dosage forms (EMA/CPMP/EWP/280/96 Corr1) states that the regulatory criteria applied for biphasic modified release products should follow the criteria applied for the prolonged release phase with additional pharmacokinetic parameters (partial AUC and C_{max}). The approach of applying the requirements for a single unit formulation (6.1.1 of the guideline) and perform one study under fed conditions is considered adequate, with the justification for waiving provided above.

Moreover, it appears that the prolonged release part of the formulation is not significantly affected by food, which is confirmed by the similar results obtained in the studies with the 54 mg strength in fasting and fed conditions, respectively, for both the test and reference product. Therefore, it is expected that similar results would be obtained in studies under fed conditions with the lower strengths as it was obtained in the studies under fasting conditions for these strengths. The in vitro dissolution results also confirm that there is no food effect, since the dissolution is not affected by different pH within the physiological range or by applying FeSSGF or FeSSIF dissolution media for any of the strengths.

Regarding the immediate release part of the formulation the waiver criteria for this part is also considered fulfilled as proportional compositions is used for this part of the formulation. The outer layer of the formulation is dissolved and the highly soluble methylphenidate is released immediately.

Based on the discussion above, the CHMP accepted the arguments provided by the applicant/MAH and agreed that the waiver of the studies under fed conditions for the lower strengths (18 mg and 36 mg) is justified.

Grounds for positive opinion

Whereas

- The Committed considered the notification of the referral triggered by Denmark under Article 29(4) of Directive 2001/83/EC. The Netherlands and Germany considered that the granting of the marketing authorisation constitutes a potential serious risk to public health.
- The Committed reviewed all the data submitted by the applicant in order to support the bioequivalence between Methylphenidate Sandoz 18 mg, 36 mg, 54 mg prolonged release tablets and the reference product.
- The Committee is of the opinion that bioequivalence was demonstrated under fasting conditions for the immediate and prolonged release phase and under fed conditions for the prolonged release phase.
- The Committee acknowledged that the conventional criteria for bioequivalence were not met for the immediate release phase in the fed study. However, the Committee is of the opinion that the observed deviation is attributed to variability between subjects and to physiological conditions after intake of a high fat meal and this does not translate into differences in quality between Methylphenidate Sandoz and the reference formulations.
- The Committee is of the opinion that the waiver of the studies under fed conditions for the lower strengths (18 mg and 36 mg) is justified.

the CHMP has recommended the granting of the marketing authorisations for which the summary of product characteristics, labelling and package leaflet remain as per the final versions achieved during the Coordination group procedure as mentioned in Annex III for Methylphenidate Sandoz and associated names (see Annex I).