25 July 2013
EMA/596774/2013

Assessment report pursuant to Article 29(4) of Directive 2001/83/EC

Methylphenidate Sandoz

INN: methylphenidate hydrochloride

Applicant / Marketing authorisation holder: Sandoz A/S

Procedure no: EMEA/H/A-29/1359

Note

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

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1. Background information on the procedure

1.1. Mutual recognition procedure (MRP) and CMD(h) 60 day procedure

Sandoz A/S submitted an application for a repeat-use mutual recognition procedure (MRP) of Methylphenidate Sandoz and associated names, prolonged-release tablet 18 mg, 36 mg, 54 mg on the basis of the marketing authorisation granted by the Reference Member State (RMS) Denmark on 29 March 2012.

The legal basis under which the authorisation was granted is an Article 10.1 of Directive 2001/83/EC.

The repeat-use MRP application was submitted to the Concerned Member States (CMS): Belgium, Germany, France, Luxembourg, Malta, The Netherlands, Sweden and United Kingdom.

The CMS involved in the first wave decentralised procedure (DCP) were: Cyprus, Spain, Finland, Poland, Portugal, Iceland and Norway.

The names and MAHs of this medicinal product currently authorised following previous MRPs are listed in Annex I.

The repeat-use MRP DK/H/2028/001-003/E/002 started on 27 June 2012.

On day 90, major issues on bioequivalence, raised by Germany and the Netherlands, remained unsolved; hence the procedure was referred to the Co-ordination Group for Mutual Recognition and Decentralised Procedures (CMD(h)), under Article 29, paragraph 1 of Directive 2001/83/EC, by Denmark on 26 September 2012.

The CMD(h) 60 day procedure was initiated on 22 October 2012.

Day 60 of the CMD(h) procedure was on 20 December 2012, and since there could be no agreement the procedure was referred to the Committee for Medicinal Products for Human Use (CHMP).

1.2. Notification of an official referral for arbitration

Notification of a referral for arbitration, under Article 29(4) of Directive 2001/83/EC, to the CHMP was made by Denmark on 21 December 2012. Germany and the Netherlands raised public health objections to Methylphenidate Sandoz (prolonged release tablet 18 mg, 36 mg, 54 mg) as they considered that bioequivalence under fed conditions has not been demonstrated between the applied and the reference product. Furthermore, the extrapolation of the fed study conducted with the highest strength 54mg to the lower strengths was not considered acceptable.

2. Scientific discussion during the referral procedure

2.1. Introduction

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 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 $_{(0\text{-}2h)}$ ($C_{max(0\text{-}2h)}$), Area Under the Curve $_{(0\text{-}2h)}$ (AUC $_{(0\text{-}2h)}$) 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 $_{(0\text{-}2h)}$ and $C_{max(0\text{-}2h)}$). 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 (immediate and prolonged-release phase) 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.

2.2. Critical evaluation

Methylphenidate Sandoz is a biphasic modified release formulations which means that it is characterised by two phases of drug release: a first phase determined by the immediate release dose fraction to provide a therapeutic drug level shortly after administration, and a second extended release (ER) phase to provide the dose fraction required to maintain an effective therapeutic level for a prolonged period.

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.

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.

Pharmacokinetics data

Results of the bioequivalence studies

The results of the applicant/MAH's studies for the established bioequivalence criteria (90% confidence intervals (CI) for AUC and C_{max} for the entire dose interval within 0 – 24 hours) are summarised in the table 1.

The studies 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%.

Table 1: Ratio and 90% confidence intervals calculated for C_{max} and AUC of the single dose studies performed under fasted and fed conditions.

Parameter		2009-19-PRT-1, 18 mg, fasted	2009-29-PRT-1, 36 mg, fasted	2009-16-PRT-1, 54 mg, fasted	2009-18-PRT-2, 54 mg, fed
C_{max}	Ratio [%]	96.1	93.7	91.0	94.9
	90% CI [%]	**89.3 - 103.4**	**87.3 - 100.5**	**84.9 - 97.4**	**86.5 - 104.0**
AUC_{0-t}	Ratio [%]	95.8	93.5	96.0	95.3
	90% CI [%]	**93.0 - 98.8**	**90.3 - 96.7**	**92.7 - 99.3**	**90.3 - 100.6**

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.

Table 2: Ratio and 90% confidence intervals calculated for $C_{max(0-2h)}$, $AUC_{(0-2h)}$, $C_{max(2-24h)}$ and $AUC_{(2-24h)}$ of the single dose studies performed under fasted and fed conditions.

Parameter		2009-19-PRT-1, 18 mg, fasted	2009-29-PRT-1, 36 mg, fasted	2009-16-PRT-1, 54 mg, fasted	2009-18-PRT-2, 54 mg, fed
$C_{max(0-2h)}$ [1]	Ratio [%]	102.0	95.1	97.9	103.3
	90% CI [%]	**94.3 - 110.3**	**86.4 - 104.7**	**90.9 - 105.3**	**74.8 - 142.7**
$AUC_{(0-2h)}$	Ratio [%]	100.3	99.3	100.3	96.6
	90% CI [%]	**91.2 - 110.4**	**88.8 -111.0**	**90.8 - 110.7**	**60.0 - 155.6**
$C_{max(2-24h)}$ [2]	Ratio [%]	96.1	93.7	90.9	95.7
	90% CI [%]	**89.0 - 103.4**	**87.3 - 100.5**	**84.9 - 97.4**	**87.4 - 104.7**
$AUC_{(2-24h)}$	Ratio [%]	95.6	93.0	95.7	94.7

90% CI [%]	**92.8 - 98.4**	**89.9 - 96.3**	**92.4 - 99.0**	**89.6 - 100.2**

[1] Calculated as highest concentration between 0-2 hours

[2] Calculated as highest concentration between 2-24 hours

For the studies under fasted conditions, bioequivalence between Methylphenidate Sandoz and the reference product was demonstrated for the immediate and extended release-phases using the partial metrics (i.e. $C_{max(0-2h)}$, AUC $_{(0-2h)}$, $C_{max(2-24h)}$ and AUC $_{(2-24h)}$).

For the study under fed conditions, the PK parameters for the extended release-phase ($C_{max(2-24h)}$ and AUC $_{(2-24h)}$) were within the conventional criteria. However, the PK parameters for the initial phase were not within the conventional criteria of 80%-125%: $C_{max(0-2h)}$ = 74.8 -142.7 and AUC $_{(0-2h)}$ = 60.0 – 155.6 (90% CI).

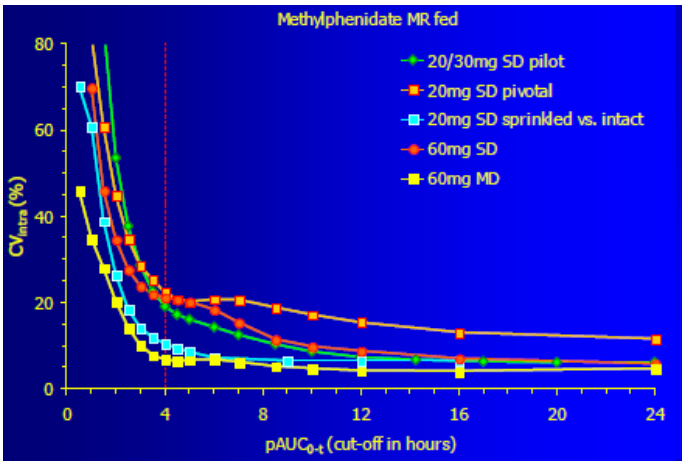
The applicant/MAH claimed that this is primarily attributed to the high intra-subject variability observed in this early phase as the point estimators $C_{max(0-2h)}$ and AUC $_{(0-2h)}$ are very close to 100% indicating that with an adequate sample size bioequivalence could have been shown also for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

Physiological conditions after intake of a high fat meal

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.

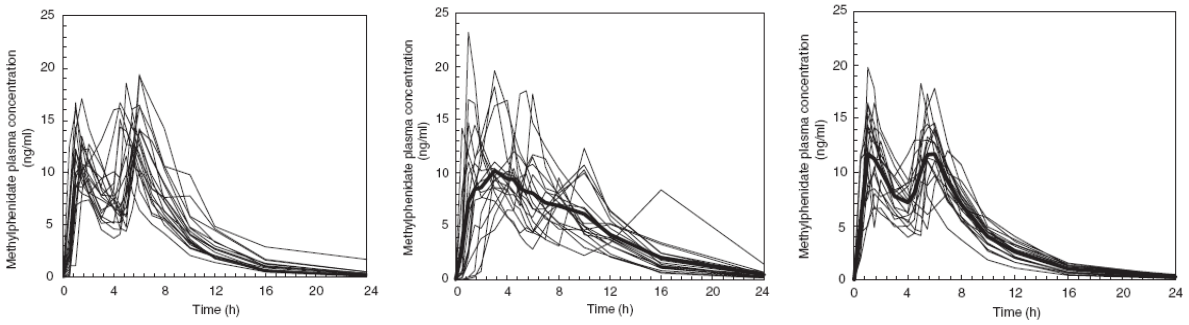
Figure 1 presents the intra-subject variability in dependence of the cut-off time of various methylphenidate ER formulations with multiphasic profiles. As can be seen, the intra-subject variability shows an exponential increase with regard to decrease in the cut-off time.

Figure 1: Within-subject variability in dependence of the cut-off time of various methylphenidate ER formulations with multiphasic profiles ["Practically meeting modified release BE requirements" BEBAC; Innovations in Modified Release Evening Seminar, Berlin, 8. November 2011].



Similar observations are reported by Lee *et al.* 2003, who 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 (see figure 2). Lee *et al.* observed that initial methylphenidate profiles were more variable between the subjects in the fed state than in the fasted state.

Figure 2: Individual profiles of Ritalin LA after administration an empty stomach (left), after a high fat meal (middle) and after administration with applesauce (right) [Lee et al, 2003].



The data obtained in the fed study (2009-18-PRT-2) when compared to the fasting study reveals that several subjects under both the test and the reference product 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 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.

In view of the above, the CHMP acknowledged that the EMA Q&A Position Paper (EMA/618604/2008 Rev. 4) concerning biphasic formulations was not taken into consideration with the design of the studies and that the conventional criteria for bioequivalence were not met for the IR phase in the fed study.

However, the CHMP concluded that the applicant/MAH provided sufficient evidence to prove that the observed deviation is attributed to variability seen 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.

Pharmaceutical data

The formulation of Methylphenidate Sandoz was developed with the goal of showing essential similarity to the reference product with regard to pharmacodynamic and pharmacokinetic properties. This is achieved by using the same drug release technology. In addition, excipients have been chosen following the reference product's formulation and only minor differences in the qualitative composition is seen between test and reference.

The immediate release is achieved by the initial drug dose in the outer drug coat, which surrounds the semi-permeable membrane. The initial drug dose itself is protected by a film coating. Both the immediate and extended release fractions are physically separated and drug release acts individually.

The applicant/MAH argued that an immediate release part and a modified-release part can be considered separate parts. It is not the modified release part that traps the immediate release part in the stomach, but this is rather the physiological conditions (the stomach contents) in the stomach under high-fat conditions. This actually leads to differences in the absorption during fasted and fed state in the first absorption phase. Therefore, from a scientific point of view, the immediate release and modified release portions can be regarded separately.

In vitro dissolution profile

To demonstrate this separation comparative in-vitro dissolution profiles of test and reference product without the immediate release coating have been compared with test and reference product (with coating) at pH 1 (Figure 3a and 3b).

Figure 3a: Dissolution profiles without (▲) and with (■) immediate release coating of 54 mg test product in pH 1.

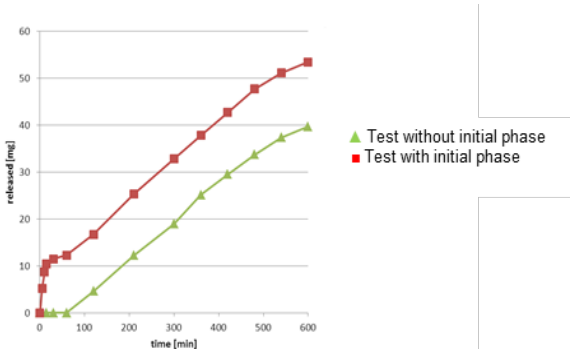
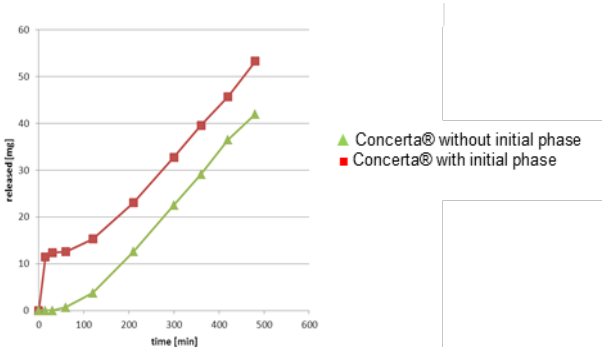


Figure 3b: Dissolution profiles without (▲) and with (■) immediate release coating of 54 mg Concerta in pH 1.



The profiles show that a lag time of approximately 60 minutes is required before the tablet core (prolonged release fraction) releases the active substance. The immediate layer dissolves rapidly (methylphenidate HCl is a Biopharmaceutics Classification System (BCS) class 1 compound (high solubility, high permeability)). Therefore, the active substance in the immediate release layer is released fast and independent from the prolonged part.

Dissolutions profiles within the physiological pH range for all strengths are comparable between test and reference product. The initial phase (0-120 min) of the dissolution profiles has been compared by calculation of f2 values. As f2 values are significantly higher than 50 for all pH values 1, 4.5 and 6.8, the similarity of the initial dose between test and reference product is demonstrated.

Additional in vitro data

To mimic the postprandial food state as close as possible to the in vivo conditions in the stomach, where the release of the initial dose takes place, the dissolution medium FeSSGF (Fed state simulated

gastric fluid) was used. The dissolution data of the applied product and reference product do not show any differences in the profiles in FeSSGF, especially within the first 120 minutes, where it is very likely that the formulations are still located in the stomach after intake of a high fat meal.

In order to investigate a probable food effect on the test product in vitro in the intestine, dissolution profiles of the 54 mg strength of the applied product were compared in FeSSIF (Fed state simulated intestinal fluid) against standard pH 6.8 buffer. The dissolution comparison demonstrates that there is no influence of the fed state medium in the intestine on the dissolution performance of the formulations.

Investigations in FeSSGF and FeSSIF demonstrate that there is no influence of the fed state on the test formulation. It was concluded that similar performance of the test and reference product in vitro is proven.

Based on the discussion above, the CHMP 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.

Based on the bioequivalence study carried out under fed conditions with the 54 mg strength, waiver of studies under fed conditions for the 18 and 36 mg 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 show 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.

2.3. Risk management plan

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

2.4. Recommendation

Based on the pharmacokinetics, pharmaceutical and supporting literature data provided by the applicant/MAH, the CHMP considered that sufficient evidence have been provided to prove that high variability in the immediate release phase is due to food-induced physiological conditions and not due to differences in formulation. Furthermore, the CHMP was of the opinion that the waiver of the studies under fed conditions for the lower strengths (18 mg and 36 mg) is justified.

2.5. Conclusions and benefit risk assessment

Whereas

- The Committee 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 Committee 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 phases 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 was of the opinion that the benefit/risk ratio of Methylphenidate Sandoz and associated names is considered to be favourable. The CHMP issued a positive opinion recommending the granting of the marketing authorisation and of the summary of product characteristics, labelling and package leaflet as per the final versions achieved during the Coordination group procedure as mentioned in Annex III of the CHMP opinion.