Specialist Pharmacy Service

NHS

Extended-release methylphenidate: A review of the pharmacokinetic profiles of available products

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Background

Methylphenidate is a central nervous stimulant available in the UK in various licensed immediate, and modified-release, oral, solid dosage forms. It is a schedule 2 controlled drug, licensed for the treatment of attention deficit hyperactivity disorder (ADHD) in children aged over 6 years and adolescents[1] and is the usual first line treatment for this condition for both children and adults[2], (though initiation in adults is outside of the product licence). Most of the products available specify in their Summary of Product Characteristics (SPCs) that in patients whose symptoms persist into adulthood and who have shown clear benefit from treatment, it may be appropriate to continue treatment into adulthood [3,4,5,6]. Methylphenidate, as a stimulant, is also sometimes used off-label for disorders of excessive somnolence e.g. narcolepsy, idiopathic hypersomnia[7].

This review discusses current NICE recommendations for the use of methylphenidate for the treatment of ADHD and describes the pharmacokinetic differences between the currently available modified-release products available: Concerta XL, Delmosart XL, Equasym XL, Matoride XL, Medikinet XL, Ritalin XL, Xaggitin XL and Xenidate XL.

National Institute for Health and Care Excellence (NICE) clinical guideline NG87 on "Attention deficit hyperactivity disorder: diagnosis and management"[2]

In their clinical guideline, NICE make several recommendations regarding pharmacological management of ADHD:

- Drug treatment should be initiated by a specialist trained in the diagnosis and management of ADHD.
- Methylphenidate hydrochloride is recommended as first-line treatment. If a 6-week trial of methylphenidate hydrochloride at the maximum tolerated dose does not reduce symptoms and associated impairment, consider switching to an alternate.
- Begin with low doses of immediate-release or modified-release preparations consistent with starting doses in the BNF

Advice pertaining to modified-release methylphenidate for ADHD

The guideline recommends that modified-release preparations may be considered for the following reasons:

- Convenience
- Improving adherence
- Reducing stigma (because the child or young person does not need to take medication at school)
- Reducing problems of storing and administering controlled drugs at school
- The risk of stimulant misuse and diversion with immediate-release preparations

Modified-release preparations should be given as a single dose in the morning (or no more than twice a day in adults) and immediate-release preparations should be given in two or three divided doses (or up to four times a day in adults).

The committee agreed that prescribers should be familiar with the pharmacokinetic profiles of all the modified-release and immediate-release preparations available for ADHD to ensure that treatment is tailored effectively to the individual's needs. Following titration and dose stabilisation, prescribing and monitoring should be carried out under locally agreed shared care arrangements with primary care. The guideline also recommends that healthcare

professionals must take account of variations in bioavailability or pharmacokinetic profiles of different preparations to avoid reduced effect or excessive adverse effects.

For adult patients, modified-release preparations may be preferred to increase adherence and in circumstances where there are concerns about substance misuse or diversion. The guideline makes no specific suggestions relating to the choice of the various extended-release formulations of methylphenidate.

Modified-release methylphenidate preparations currently available in the UK

The following preparations are currently licensed in the UK:

- Concerta XL tablets
- Delmosart XL tablets
- Equasym XL capsules
- Matoride XL tablets
- Medikinet XL capsules
- Ritalin XL capsules
- Xaggitin XL tablets
- Xenidate XL tablets

All the modified-release methylphenidate preparations include an immediate-release component as well as an extended-release component. This allows for rapid onset of action while avoiding the need to take further doses during the day to maintain effect.

The biphasic release profiles of these products are however not all equivalent and contain different proportions of the immediate-release and modified-release component. The BNF states that "different versions of modified-release preparations may not have the same clinical effect. To avoid confusion between these different formulations of methylphenidate prescribers should specify the brand to be dispensed"[1].

Of the modified-release preparations, Delmosart XL, Matoride XL, Xaggitin XL and Xenidate XL tablets have been approved based on bioequivalence data compared to Concerta XL tablets. These tablets therefore have a release profile similar to Concerta XL tablets.

Separately, Equasym XL, Medikinet XL and Ritalin XL capsules have a different ratio of immediate-release/extended-release components compared to Concerta XL tablets and also have a different release profile in relation to Concerta XL tablets. The key features of these four products have been described below and summarised in the table that follows.

Concerta XL tablets[3]

Concerta XL was licensed in the UK in February 2002. It is an oral tablet with an osmotic release system and has internal layers of extended-release methylphenidate, surrounded by a coat of immediate-release methylphenidate. The non-absorbable membrane of the tablet can pass into the faeces unchanged. It is available as 18mg, 27mg, 36mg and 54mg tablets. The manufacturers advise that when initiating, titration should be started at 18mg and proceed with 18mg increments at approximately weekly intervals[3]. The 27mg dose is available for those who wish to prescribe between the 18mg and 36mg doses. When converting patients to Concerta XL from methylphenidate immediate release, the manufacturers recommend a conversion factor of 18mg Concerta XL per 15mg methylphenidate immediate release daily dose. The maximum daily dosage recommended by the manufacturer is 54mg.

Equasym XL capsules[4]

Equasym was licensed in the UK in February 2005. Each capsule contains beads coated with immediate release or extended release methylphenidate. It is available as 10, 20 and 30mg capsules. When initiating methyphenidate with Equasym XL the manufacturers recommend starting at 10mg once daily, increasing as necessary by weekly increments of 5-10mg[9]. The manufacturers recommend that when converting from immediate release methylphenidate, the total daily dose can be converted 1:1 to Equasym XL[9]. The maximum daily dosage recommended by the manufacturer is 60mg[9].

Medikinet XL capsules[5]

Medikinet XL was licensed in the UK in February 2007. These capsules contain immediate release uncoated pellets and extended release coated pellets producing a two-stage release profile. Medikinet XL capsules are available as 5mg, 10mg, 20mg, 30mg, 40mg, 50mg and 60mg. When initiating methylphenidate with Medikinet XL, the manufacturers recommend starting at 10mg once daily, increasing as necessary by weekly increments of 5-10mg. The manufacturers recommend that when converting from immediate release methylphenidate, the total daily dose can be converted 1:1 to Medikinet XL. The maximum daily dosage recommended by the manufacturer is 60mg[4].

Ritalin XL capsules[6]

Although Ritalin XL was licensed in December 2017, it was launched in the UK in 2020. These capsules contain immediate release beads and extended release beads producing a two-stage release profile. Ritalin XL capsules are available as 10mg, 20mg, 30mg, 40mg, 50mg and 60mg capsules, with a recommended starting dose of 10mg in the morning (based on clinical judgement).

Bioavailability of Ritalin XL 20mg was compared with that of Concerta XL 18mg in a small, crossover study (n=28) in healthy individuals. Ritalin XL exhibited a bimodal plasma-concentration-time profile with peaks at 2.1 and 5.6 hours post dosing, whilst Concerta XL produced peaks at 3.3 and 6.4 hours respectively. Separately, a bioavailability study comparing Ritalin XL with Medikinet XL (n=26) showed a comparable bimodal plasma-concentration-time profile for both in the fed state only.

Comparison of pharmacokinetic profiles of Concerta XL[3], Medikinet XL[5], Equasym XL[4] and Ritalin XL[6] capsules

	Concerta XL tablets	Medikinet XL capsules	Equasym XL capsules	Ritalin XL capsules
Composition (percentage immediate/extended release)	22/78	50/50	30/70	50/50
Release profile	Maximum plasma concentration at 1-2 hours, second peak at 6-8 hours	Maximum plasma concentration reached rapidly, second peak at 3-4 hours	Maximum plasma concentration at 1.5 hours, followed by a second peak at 6 hours followed by a gradual decline	Maximum plasma concentration at 1-2 hours, second peak at 4 hours
Duration of action	Up to 12 hours	Up to 8 hours	Up to 8 hours	Up to 8 hours
Administration	Swallow whole with liquid. Must not be chewed, crushed or divided	Can be swallowed whole with liquid, or opened and the contents sprinkled onto a small amount (tablespoon) of applesauce or yoghurt and given immediately Capsules and contents not to be crushed or chewed	Can be swallowed whole with liquid, or opened and the contents sprinkled onto a small amount (tablespoon) of applesauce or yoghurt and given immediately. Capsules and contents not to be crushed or chewed	Can be swallowed whole with liquid, or opened and the contents sprinkled onto a small amount (tablespoon) of applesauce or yoghurt and given immediately. Capsules and contents not to be crushed or chewed
Food requirements	Can be given with or without food	Must be taken with or after breakfast¥	To be taken with or after breakfast*	Can be taken with or without food
Frequency	Once daily in the morning	Once daily in the morning	Once daily in the morning	Once daily in the morning
Immediate-release methylphenidate equivalent	Three times daily	Twice daily	Twice daily	Twice daily

¥ Medikinet XL has to be taken with or after a meal in order to obtain sufficiently prolonged action and to avoid high plasma peaks. Methylphenidate hydrochloride is absorbed much faster from Medikinet XL when the medicinal product is taken on an empty stomach. In this case, release may not be adequately sustained. Therefore Medikinet XL should not be administered without food.

*Ingestion together with food with a high fat content delays absorption of Equasym XL (Tmax) by approximately one hour and increases the maximum concentration (Cmax) by approximately 30% and the amount absorbed (AUC) by approximately 17%.

The differing time–action profiles provided by these long-acting formulations may allow clinicians to target specific periods of the day that are particularly relevant for a patient, facilitating individualisation of ADHD treatment.

Generic preparations approved based on bioequivalence studies comparing products with Concerta XL tablets

Concerta XL® modified-release tablets[3] (lactose-containing [a])	18mg, 27mg, 36mg, 54mg
Delmosart XL ® modified-release tablets[7] (lactose-containing [a])	18mg, 27mg, 36mg, 54mg
Matoride XL® modified-release tablets[8] (lactose-containing [a])	18mg, 36mg, 54mg (27mg strength not available)
Xaggitin XL® modified-release tablets[9] (lactose-containing [a])	18mg, 27mg, 36mg, 54mg
Xenidate XL® modified-release tablets[10] (sucrose containing [b])	18mg, 27mg, 36mg, 54mg

[a]Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.
[b]Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

All tablets (except Xenidate XL 18mg - round) are presented as biconvex capsule-shaped tablets. All products with the 18mg strength are yellow, all products with the 27mg strength are grey (except Xenidate XL which is yellow), all products with the 36mg strength are white, and all products with the 54mg strength are red-brown in colour.

In order to demonstrate bioequivalence, pharmacokinetic trials need to show that the upper and lower limits of the 90% confidence intervals for both the maximal concentration after dosing (Cmax) and the area under curve of plasma level vs time (AUC) do not fall outside of the range of 80%-125% of the value for the reference product[11]. As the comparator product in this instance has a biphasic release profile bioequivalence had to be demonstrated for both phases (i.e. initial phase Cmax and AUC, and second phase Cmax and AUC).

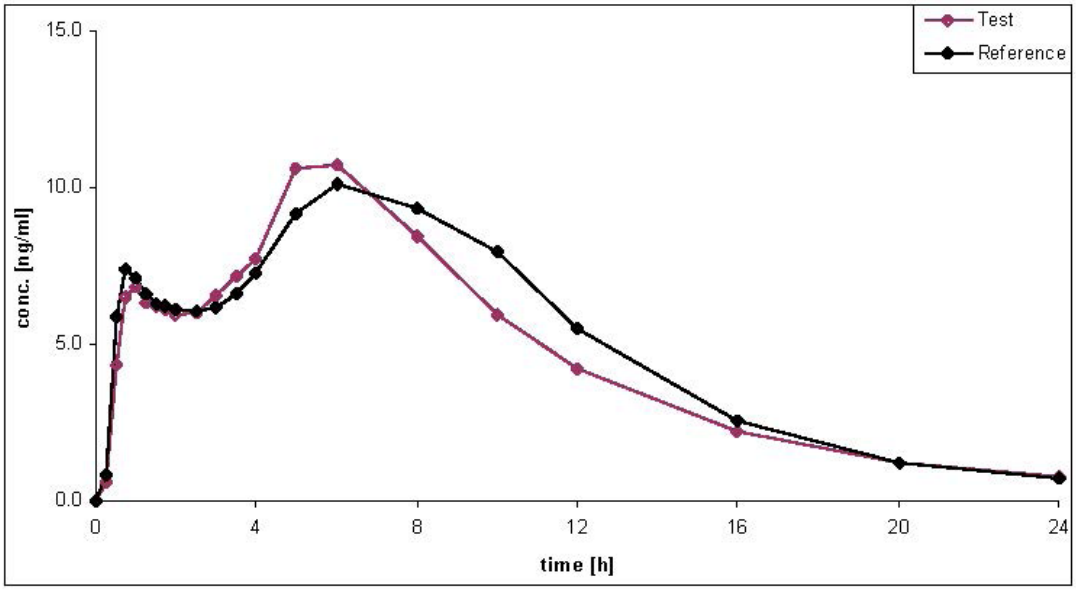
Bioequivalence data for products with similar ratio of immediate- /prolonged-release characteristics to Concerta XL tablets

Xenidate XL bioequivalence studies[12]

The comparative bioavailability of Xenidate XL tablets to Concerta XL tablets was studied under both fasting and fed state at the 54mg dose as part of a crossover study (n=52). Sampling for one dose was deemed sufficient for licence for the range of doses[11].

Fasted state results:

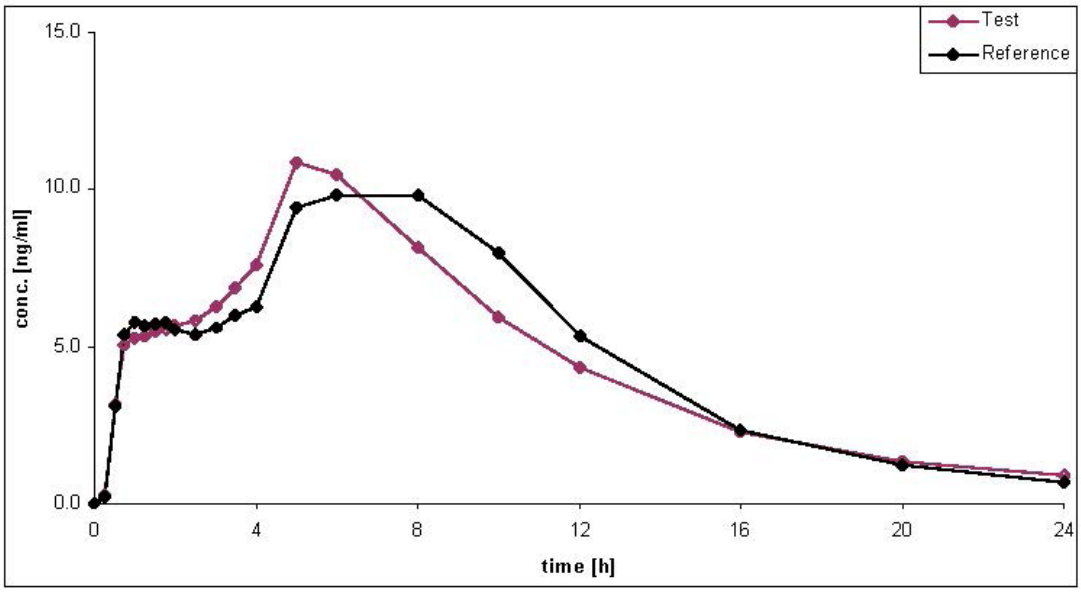
Parameter	Ratio (Xenidate XL /Concerta XL)	90% CI
$AUC_{0—2.5h}$	99.03%	92.57 - 105.94
$AUC_{2.5\text{-}24h}$	93.79%	89.74 - 98.01
$Cmax_{0\text{-}2.5h}$	94.92%	89.52 - 100.66
$Cmax_{2.5\text{-}24h}$	104.16%	98.63 - 110.00



Mean (arithmetic mean) plasma concentration-time curves of methylphenidate after administration of the test product and the reference product (N = 12)

Fed state results

Parameter	Ratio (Xenidate XL /Concerta XL)	90% CI
$AUC_{0—2.5h}$	99.75%	87.94-113.14
$AUC_{2.5-24h}$	92.21%	90.20-94.27
$Cmax_{0-2.5h}$	90.50%	82.97-98.72
$Cmax_{2.5-24h}$	97.27%	94.18-100.46



Mean (arithmetic mean) plasma concentration-time curves of methylphenidate after administration of the test product and the reference product (N = 52)

As the 90% confidence intervals for the parameters $AUC_{0—2.5h}$, $AUC_{2.5-24h}$, $Cmax_{0-2.5h}$ and $Cmax_{2.5-24h}$ all lay between 80-125% for both the fasted and fed state the Xenidate XL product was given marketing authorisation. This was granted for all strengths of the product.

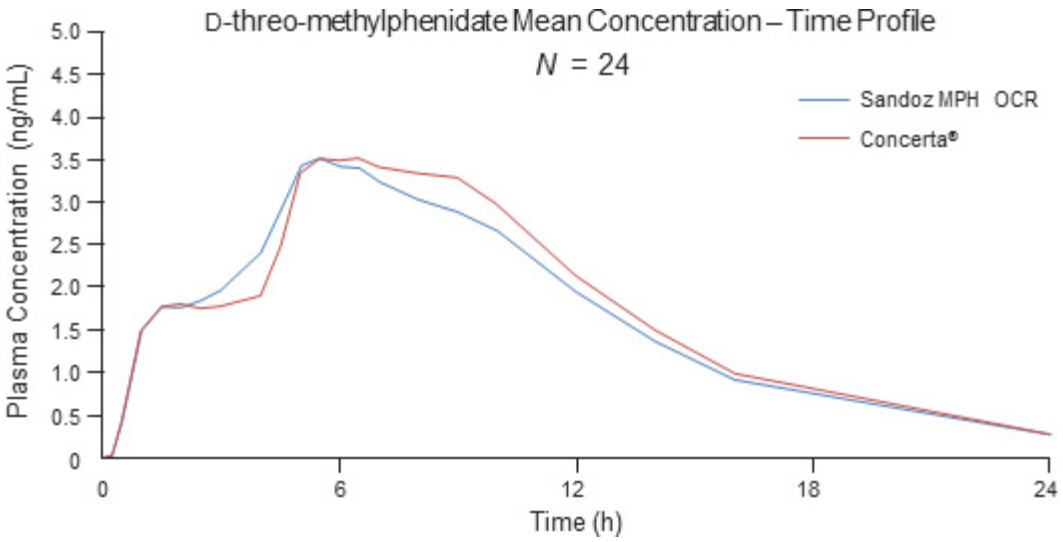
Matoride XL bioequivalence studies[13]

Four separate crossover studies were performed: Matoride XL 54mg, 36mg and 18mg vs Concerta XL 54mg, 36mg and 18mg (n= 24, 22 and 24 respectively) under fasting conditions, and Matoride XL 54mg vs Concerta XL 54mg under fed conditions (n=21). The outcomes are described below:

Fasted state results

Parameter	Ratio at 18mg	90% CI	Ratio at 36mg	90% CI	Ratio at 54mg	90% CI
$AUC_{0—2h}$	100.30%	91.15-110.36	99.29%	88.82-110.99	100.29%	90.83-110.73
AUC_{2-24h}	95.58%	92.81-98.44	93.03%	89.85-96.32	95.67%	92.44-99.01
$Cmax_{0-2h}$	101.99%	94.28-110.33	95.11%	86.36-104.74	97.88%	90.95-105.33
$Cmax_{2-24h}$	96.08%	89.94-97.40	93.69%	87.31-100.54	90.96%	84.94-97.40

Under fed conditions only 50% of the profiles of both Concerta XL and Matoride XL were biphasic (the rest were continuous release). Therefore separation of the 2 phases was not possible and bioequivalence would therefore be demonstrated by Cmax and $AUC_{0—t}$ equivalence.



Fed state results:

Parameter	Ratio	90% CI
$AUC_{0—t}$	99.75%	87.94 - 113.14
AUC_{0-inf}	92.21%	90.20 - 94.27
Cmax	90.50%	82.97 - 98.72

Delmosart XL bioequivalence studies[14]

Four studies were carried out to confirm the bioequivalence between Delmosart XL® 18mg, 27mg, 36mg and 54mg prolonged-release tablets and Concerta® XL 18mg, 27mg, 36mg and 54mg prolonged-release tablets. Two studies, one fed and one fasted, were carried out for each of the 18mg and 54mg strengths. The studies reported by the manufacturer are the same as the studies for Xaggitin XL and it appears both these products are identical branded generics of the reference product Concerta XL.

Xaggitin XL bioequivalence studies[15]

Xaggitin XL prolonged-release methylphenidate tablets are a branded generic version of Concerta XL. The tablets have a biphasic release profile, with the formulation containing an immediate-release component of 25% and a prolonged-release component of 75% (Concerta XL contains an immediate-release component of 22% and a prolonged-release component of 78%). Four studies were carried out to confirm the bioequivalence between Xaggitin XL® 18mg, 27mg, 36mg and 54mg prolonged-release tablets and Concerta® XL 18mg, 27mg, 36mg and 54mg prolonged-release tablets. Two studies, one fed and one fasted, were carried out for each of the 18mg and 54mg strengths. The mean plasma concentrations of methylphenidate versus time curves for the 18 and 54mg strengths are shown below:

An open-label, laboratory-blind, three-treatment, randomised, three-period, crossover study in order to assess bioequivalence following single dose administration of methylphenidate hydrochloride 18mg prolonged-release tablets (test 1) and methylphenidate hydrochloride 18mg prolonged-release tablets (Test 2) versus Concerta® 18 mg prolonged-release tablets (reference) in healthy volunteers under **fasting** conditions (Study CM-365). Both test products passed the bioequivalence criteria and test 1 formulation was selected as the final test product.

Average pharmacokinetic profiles of test and reference products in study CM-365. The dotted red line represents splitting for partial AUC's.

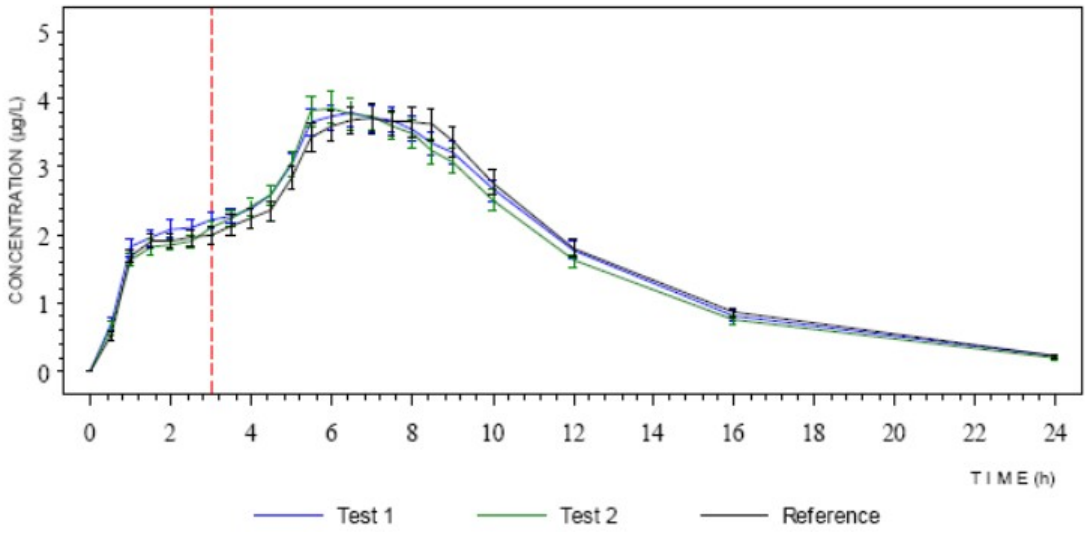


Table of results for Test 1 in study CM-365

Parameter	Ratio	90% CI
$AUC_{(0-3)}$	106.27	97.57 – 115.75
$AUC_{(3-t)}$	100.42	95.46 – 105.65
$Cmax_{(0-3)}$	106.60	98.65 – 115.20
$Cmax_{(3-t)}$	104.11	96.04 – 112.87
$AUC_{(0-t)}$	101.32	96.56 – 106.32
$AUC_{(0-inf)}$	101.28	96.52 – 106.28

Study No: CM-364 – 18mg fed study

An open-label, laboratory-blind, three-treatment, randomised, three-period, crossover study in order to assess bioequivalence following single dose administration of methylphenidate hydrochloridel 18mg prolonged-release tablets (Test 1) and methylphenidate hydrochloride 18mg prolonged-release tablets (Test 2) versus Concerta 18 mg prolonged-release tablets (reference) in healthy volunteers under **fed** conditions. Both test products passed the bioequivalence criteria and test 1 formulation was selected as the final test product.

Average pharmacokinetic profiles of test and reference products in study CM-364. The dotted red line represents splitting for partial AUC's.

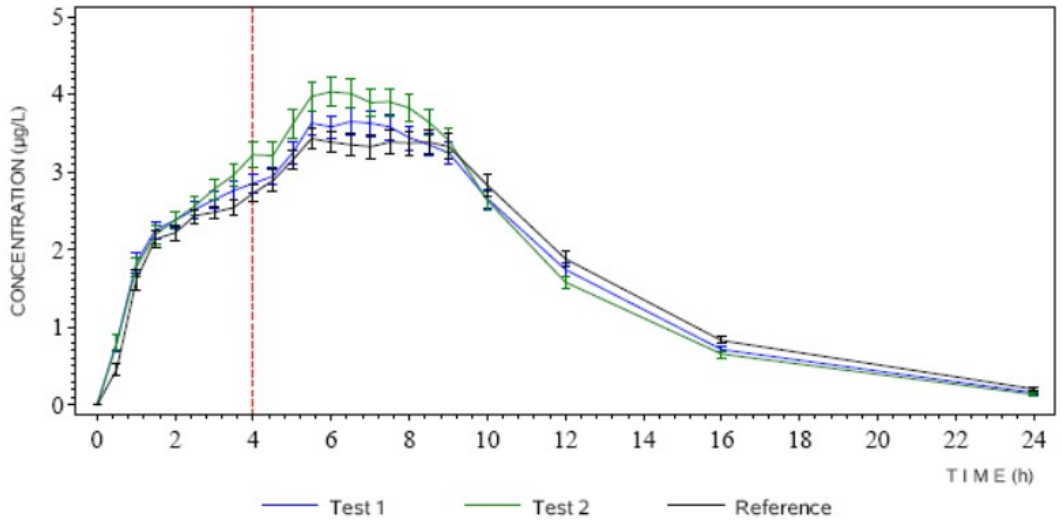


Table of results for Test 1 in study CM-364

Parameter	Ratio	90% CI
$AUC_{(0-4)}$	108.18	101.95 – 114.79
$AUC_{(4-t)}$	97.19	92.64 – 101.97
$Cmax_{(0-4)}$	103.95	98.60 – 109.59
$Cmax_{(4-t)}$	106.68	100.89 – 112.80
$AUC_{(0-t)}$	99.73	95.89 – 103.72
$AUC_{(0-inf)}$	99.42	95.63 – 103.36

Study No: CM-355 – 54mg fasting study

A single center, single-dose, open-label, laboratory-blind, randomised, two-period, two-sequence, crossover study to determine the bioequivalence of two prolonged-release tablet products containing methylphenidate hydrochloride 54 mg in up to 36 healthy male and female subjects under fasting conditions. This study was conducted with a single test product. The test product passed the bioequivalence criteria.

Average pharmacokinetic profiles of test and reference products in study CM-355. The dotted red line represents splitting for partial AUC's.

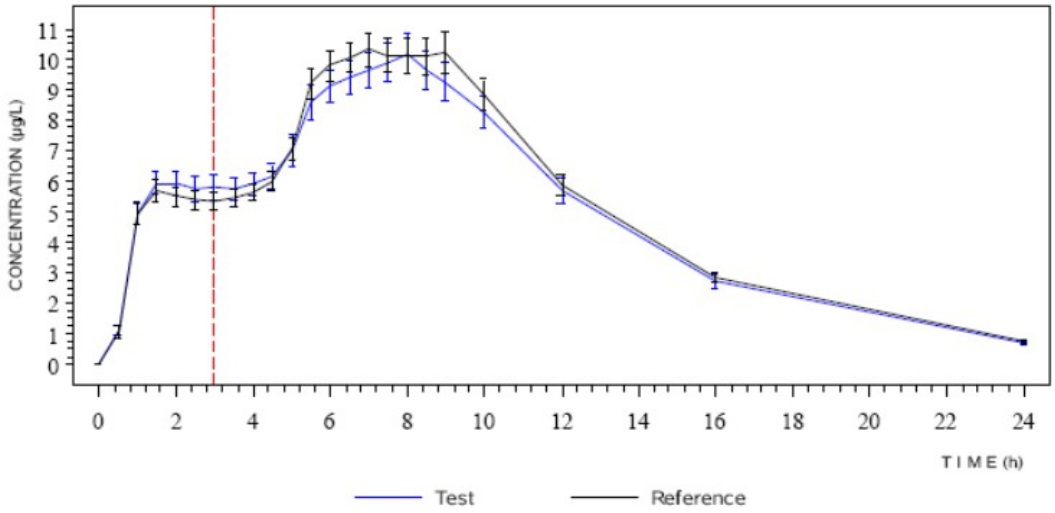


Table of bioequivalence results for study CM-355

Parameter	Ratio	90% CI
$AUC_{(0-3)}$	104.30	98.13 - 110.86
$AUC_{(3-t)}$	95.21	91.59 - 98.97
$Cmax_{(0-3)}$	103.23	96.74 - 110.16
$Cmax_{(3-t)}$	98.18	92.57 - 104.14
$AUC_{(0-t)}$	96.15	92.74 - 99.69
$AUC_{(0-inf)}$	95.87	92.37 - 99.49

Study No: CM-354 – 54mg fed study

A single centre, single-dose, open-label, laboratory-blind, randomised, two-period, two-sequence, crossover study to determine the bioequivalence of two prolonged-release tablet products containing methylphenidate hydrochloride 54mg in up to 36 healthy male and female subjects under fed conditions. This study was conducted with a single test product. The test product passed the bioequivalence criteria.

Average pharmacokinetic profiles of test and reference products in study CM- 354. The dotted red line represents splitting for partial AUC's.

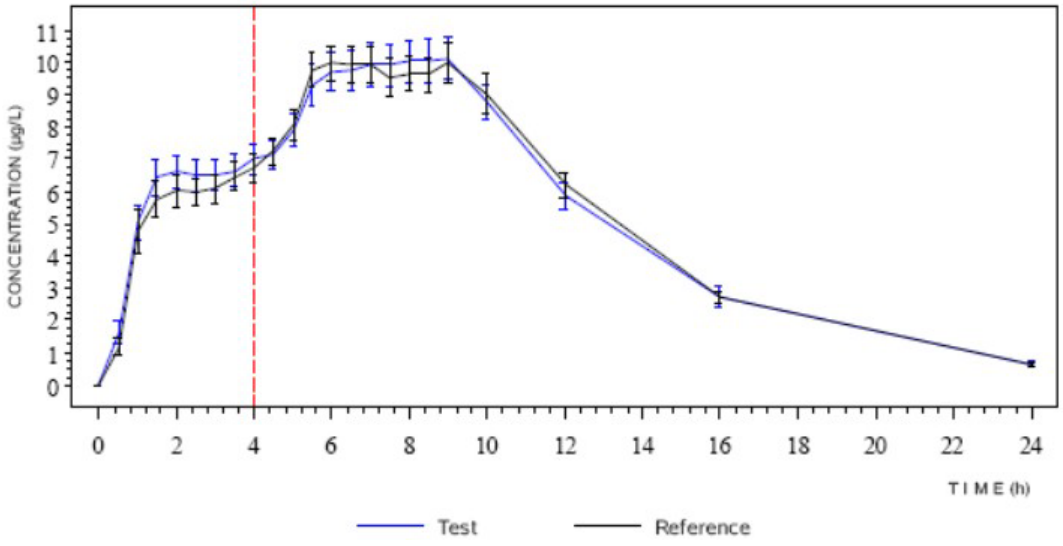


Table of bioequivalence results for study CM-354

Parameter	Ratio	90% CI
$AUC_{(0-4)}$	109.99	100.72 - 120.12
$AUC_{(4-t)}$	97.26	93.51 - 101.15
$Cmax_{(0-4)}$	109.25	101.10 - 118.06
$Cmax_{(4-t)}$	103.25	97.73 - 109.08
$AUC_{(0-t)}$	99.68	96.41 - 103.06
$AUC_{(0-inf)}$	100.89	96.49 - 105.48

Treatment cost

NHS cost of 30-dose units for the tablets[1] (£)

Product	18mg	27mg	36mg	54mg
Concerta XL	31.19	36.81	42.45	73.62
Delmosart XL	15.57	18.39	21.21	36.79
Matoride XL	15.58	Not available	21.22	36.80
Xenidate XL	15.57	18.39	21.21	36.80
Xagittin XL	15.58	18.40	21.22	36.79

NHS cost of 30-dose unit of Medikinet XL, Equasym XL and Ritalin XL capsules[1] (£)

Product	5mg	10mg	20mg	30mg	40mg	50mg	60mg
Medikinet XL	24.04	24.04	28.86	33.36	57.72	62.52	67.32
Equasym XL	Not available	25.00	30.00	35.00	Not available	Not available	Not available
Ritalin XL	Not available	23.92	28.72	33.49	57.43	Not available	66.98

Clinical implications

The separate release profiles of the Equasym XL, Medikinet XL, Ritalin XL and Concerta XL allows prescribers a choice of preparations to match a patient's needs. For example Concerta XL may be preferable for patients with evening symptoms due to the larger proportion of sustained release component and longer duration of effect, whereas the other products may be preferred in patients that might have a potential to suffer from insomnia, as it has a shorter duration of effect and higher proportion of immediate release component. In order to ensure that the correct product is dispensed it is important that the prescriber specifies the brand on the prescription.

It is clear that Delmosart XL, Matoride XL, Xaggitin XL and Xenidate XL have been granted replicate marketing authorisation to Concerta XL on the basis that they have satisfied the criteria for equivalent release profile for the reference Concerta XL product. It would seem appropriate for these branded generics to be considered as alternatives to Concerta XL when initiation of Concerta XL is appropriate. As per BNF advice, prescribers should specify the brand when prescribing Delmosart XL, Matoride XL, Xaggitin XL or Xenidate XL to ensure the correct product is dispensed.

These products match Concerta XL in terms of colouring for each prescribable dose. If there is an intention to switch patients from Concerta XL to any of the branded generics, it would be prudent for there to be a discussion with the patient or guardian to ensure that they are aware and happy with the change in preparation.

A PrescQIPP[15] review of prescribing in attention-deficit hyperactivity disorder (published November 2016, before the launch of Delmosart XL and Xaggitin XL) suggests "policy makers should consider the cost difference in primary care of the various modified release methylphenidate preparations when making formulary decisions. Including Xenidate XL® or Matoride XL® tablets on formularies where Concerta XL® would have been considered appropriate could release savings when new patients are initiated on treatment. There may also be scope to review and consider switching the medication of those already established on Concerta XL®. Organisations considering a review of prescribing of Concerta XL® prescribing should ensure that the principle, process and switching methodology is agreed locally by all key stakeholders, including local specialists and GPs. Changes to medication should only be made in the context of individual review, and should be communicated and monitored appropriately".

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