ONCE-DAILY

METHYDUR

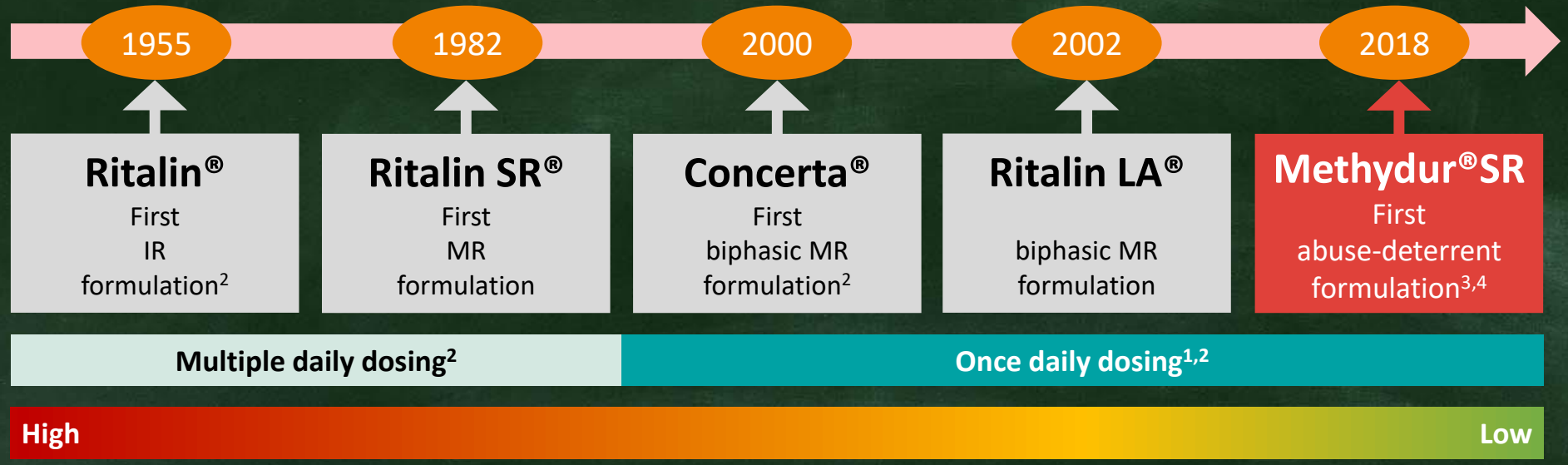
methylphenidate sustained release capsule

- ✓ **Fast onset：2 hours reach 6ng/ml**
- ✓ **Sufficient duration：8-12 hours**
- ✓ **Potential safety profiles：lower incidence of insomnia**

Milestones in the development of methylphenidate products

Several methylphenidate products have been developed to[1]:

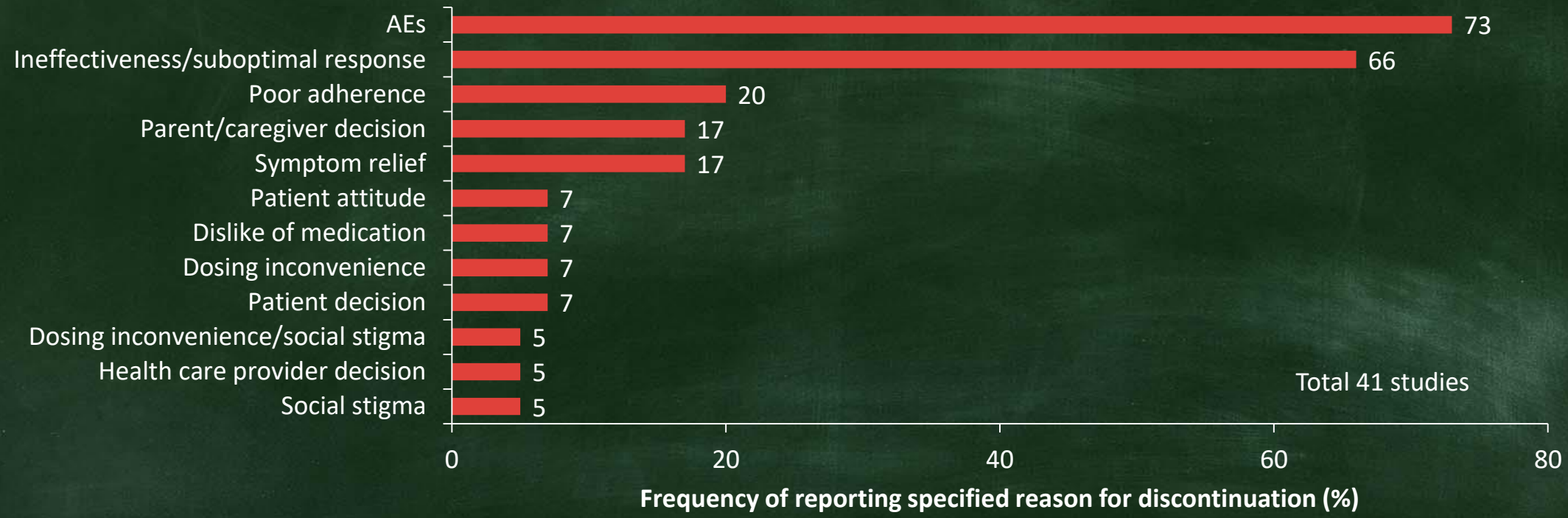
- Improve adherence
- Reduce abuse potential
- Decrease stigma associated with multiple administrations per day
- Decrease the potential for AEs related to dosage peak



AE=adverse effect; IR=immediate release; MR=modified release. 1. Cortese S, et al. CNS Drugs. 2017;31(2):149-60. 2. Patrick KS, et al. Pharmacotherapy. 2018 Oct 23. doi: 10.1002/phar.2190. 3. http://phx.corporate-ir.net/phoenix.zhtml?c=121590&p=irol-newsArticle_Print&ID=2375965 4. Data on file.

Systematic literature review:
Most frequently reported reasons for treatment discontinuation

Persistence and adherence to ADHD treatment were generally low, and **tolerability** was the most important reason for treatment discontinuation.



ADHD=attention-deficit/hyperactivity disorder; AE=adverse event.
Gajria K, et al. Neuropsychiatr Dis Treat. 2014;10:1543-69.

Effective Concentration of MPH

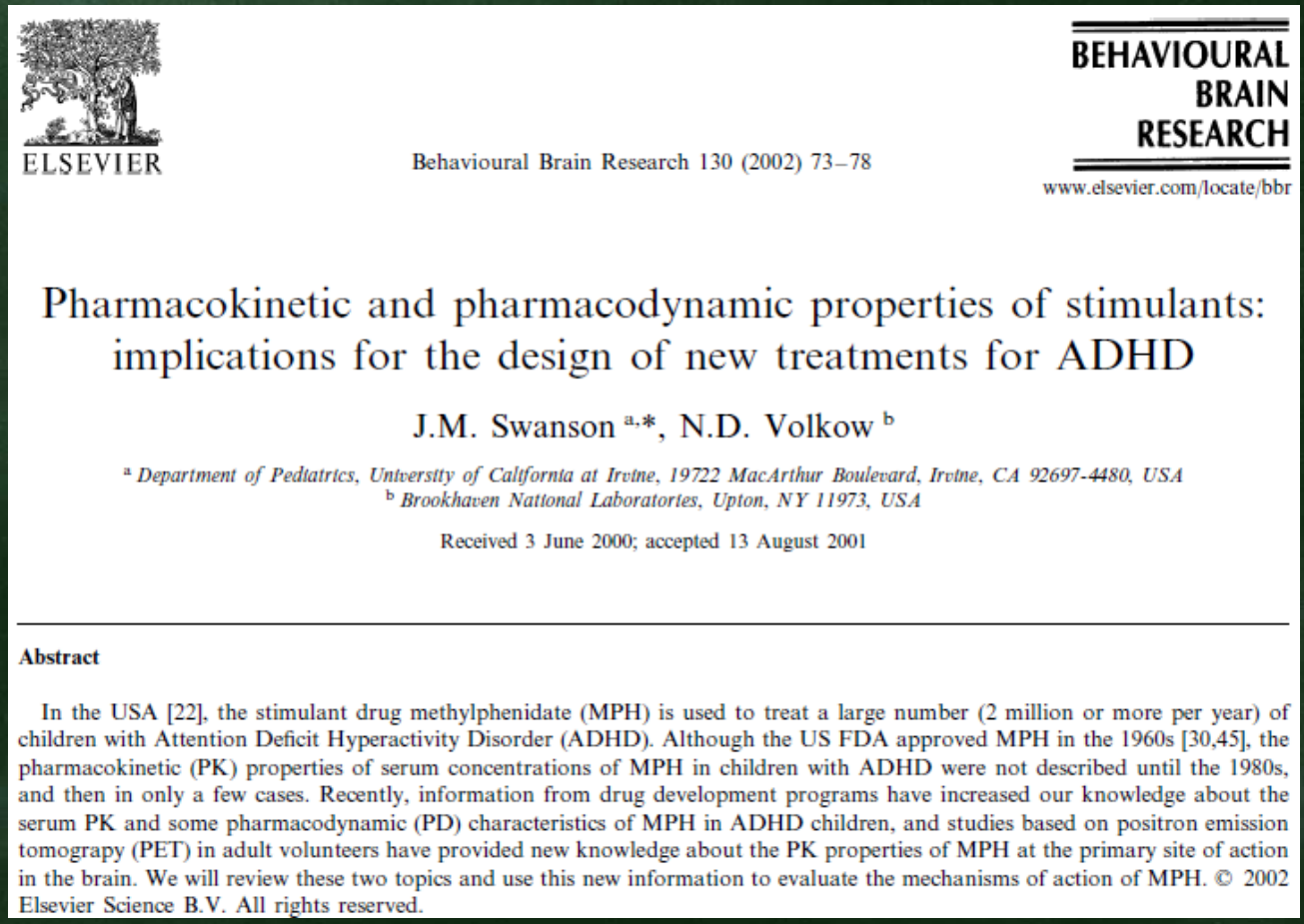
80% DAT Blockage 8–10ng/ml

PK and PD properties of stimulants: Implications for the design of new treatments for ADHD :

The **maximum MPH blockade** of DAT (80% occupancy) occurs at about **8–10 ng/ml**.

Therapeutic doses blocked 50% DAT, corresponded to **6 ng/ml**.

In human subjects, the peak **uptake of MPH in the brain was very fast** (Tmax<10 min), but the **clearance was relatively slow** (T1/2=90 min).



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Behavioural Brain Research 130 (2002) 73–78

BEHAVIOURAL BRAIN RESEARCH

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Pharmacokinetic and pharmacodynamic properties of stimulants: implications for the design of new treatments for ADHD

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Abstract

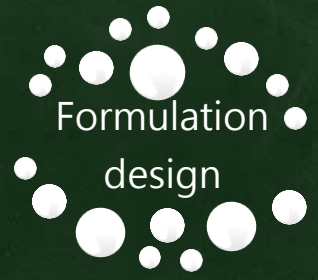
In the USA [22], the stimulant drug methylphenidate (MPH) is used to treat a large number (2 million or more per year) of children with Attention Deficit Hyperactivity Disorder (ADHD). Although the US FDA approved MPH in the 1960s [30,45], the pharmacokinetic (PK) properties of serum concentrations of MPH in children with ADHD were not described until the 1980s, and then in only a few cases. Recently, information from drug development programs have increased our knowledge about the serum PK and some pharmacodynamic (PD) characteristics of MPH in ADHD children, and studies based on positron emission tomograpy (PET) in adult volunteers have provided new knowledge about the PK properties of MPH at the primary site of action in the brain. We will review these two topics and use this new information to evaluate the mechanisms of action of MPH.

Behavioural Brain Research 2002; 130:73–78

Quality By Design

Formulation Engineering of Methydur® SR

Methydur® SR processed **5 phase I** PK and pivotal trials on research and development phase to study the pharmacologic properties, safety and optimization of capsule based on **quality by design** formulation engineering.



Formulation design

- Phase I clinical trial : PK NDA-T375-0905
- MPRT[1]
- ORADUR[2]

Prototype optimization

Phase I clinical trial : PK NDA-T375-1006

Dosage confirmation

Phase I clinical trial : PK NDA-T375-1201

Formulation confirmation

Phase I clinical trial : **PK NDA-T375-1206**

Pharmaco-kinetics and safety assessment

Phase I clinical trial : PK NDA-T375-1502

Pivotal Study

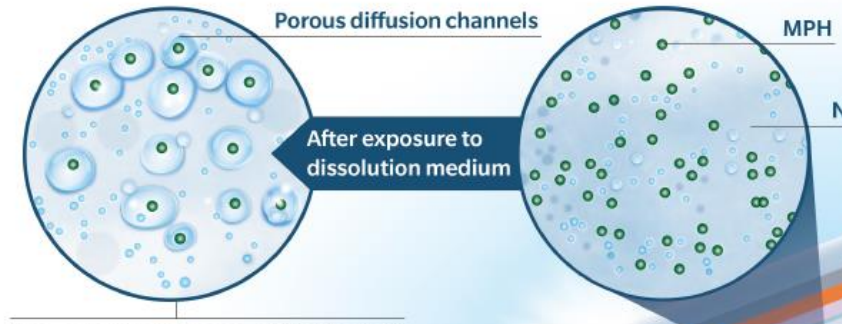
Phase III clinical trial : **OP-2PN012-301**

Data on file
[1]Patent I426897
[2]Patent TW201811328 A

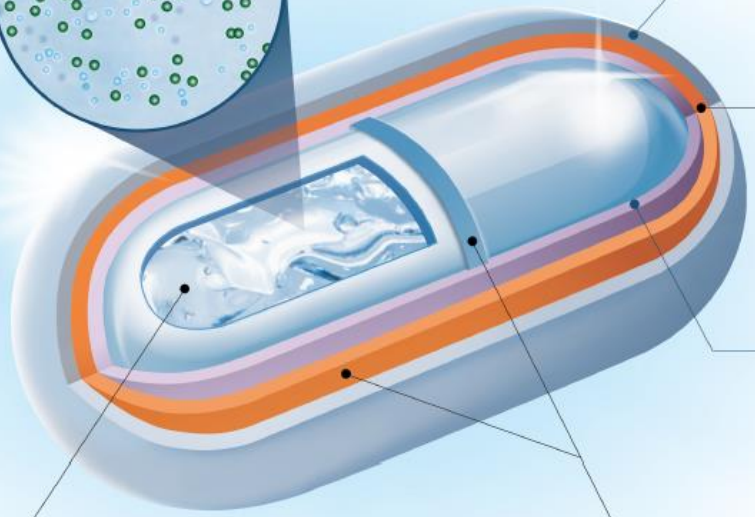
Quality By Design

ORADUR™ Technology of Methydur®SR

Design of Methydur® Sustained Release Capsules



The extended release of Methydur® (ORADUR®-MPH) is composed of non-porous continuous phase and MPH. After the capsule shell disintegrates, ORADUR®-MPH forms porous diffusion channels, and MPH is released from the channels steadily.



Layer 3: Outer layer

Different colors for different dosages.

- 44 mg – white color
- 33 mg – grey color
- 22 mg – yellow color

Layer 2: IR MPH (18%)

IR MPH is released into blood immediately for rapid symptom relief.

Layer 1: Protective coating

Delaying the release of ORADUR®-MPH.

ORADUR®-MPH (82%)

With high-viscosity base component, ORADUR®-MPH can provide sustained release of MPH for up to 12 hours.

HPMC

HPMC is the main ingredient of the capsule. HPMC is used to prevent leakage while also serving as a binder for IR MPH coating.

HPMC, hydroxypropyl methylcellulose; IR, immediate-release; MPH, methylphenidat

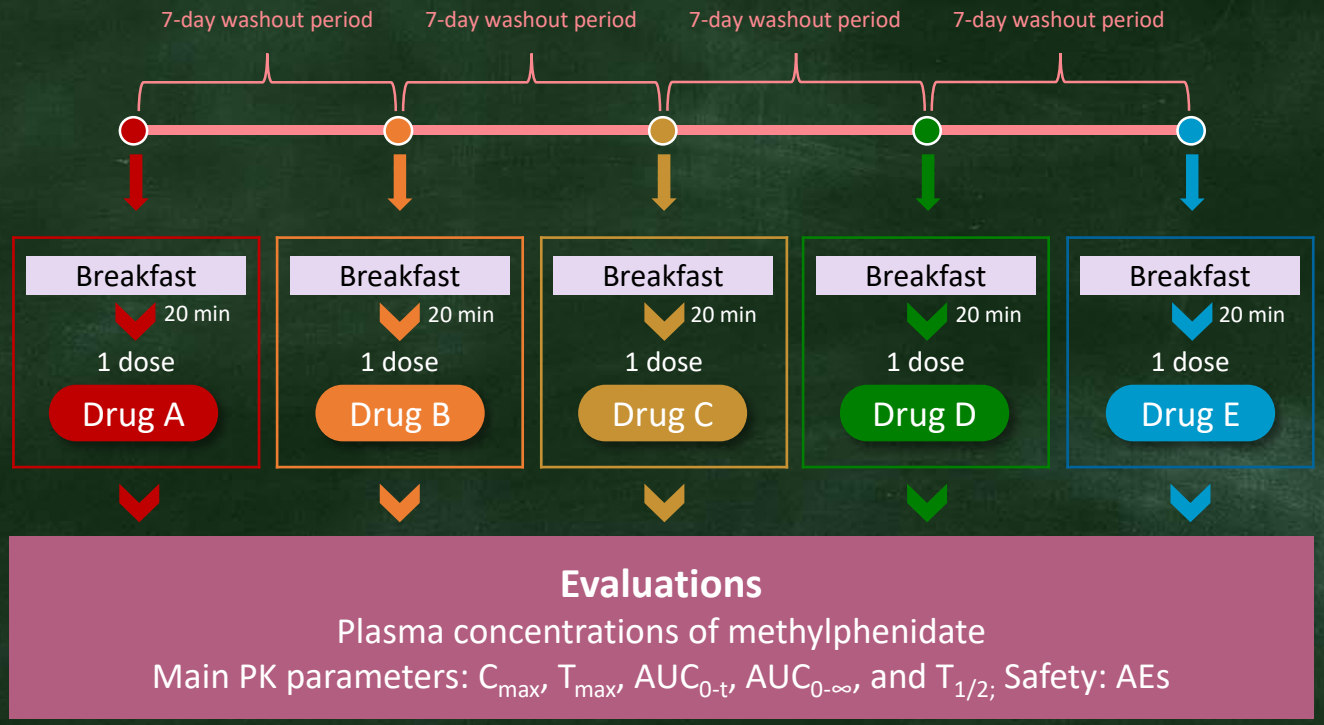
Methydur® SR Phase I Study:
PK NDA-T375-1206

Phase I, five-way crossover study to compare the PK of **Methydur® 44 mg to Concerta® 36 mg** after a single oral administration in **healthy adult** volunteers under **fed conditions**.

Healthy adult subjects
(N=15)
Age 20~45 years
BMI 18~30 kg/m^2
Body weight >50 kg

Methydur® Sustained Release Capsules 44 mg

MPH-OROS® Extended Release Tablets 36 mg
(random sequence)



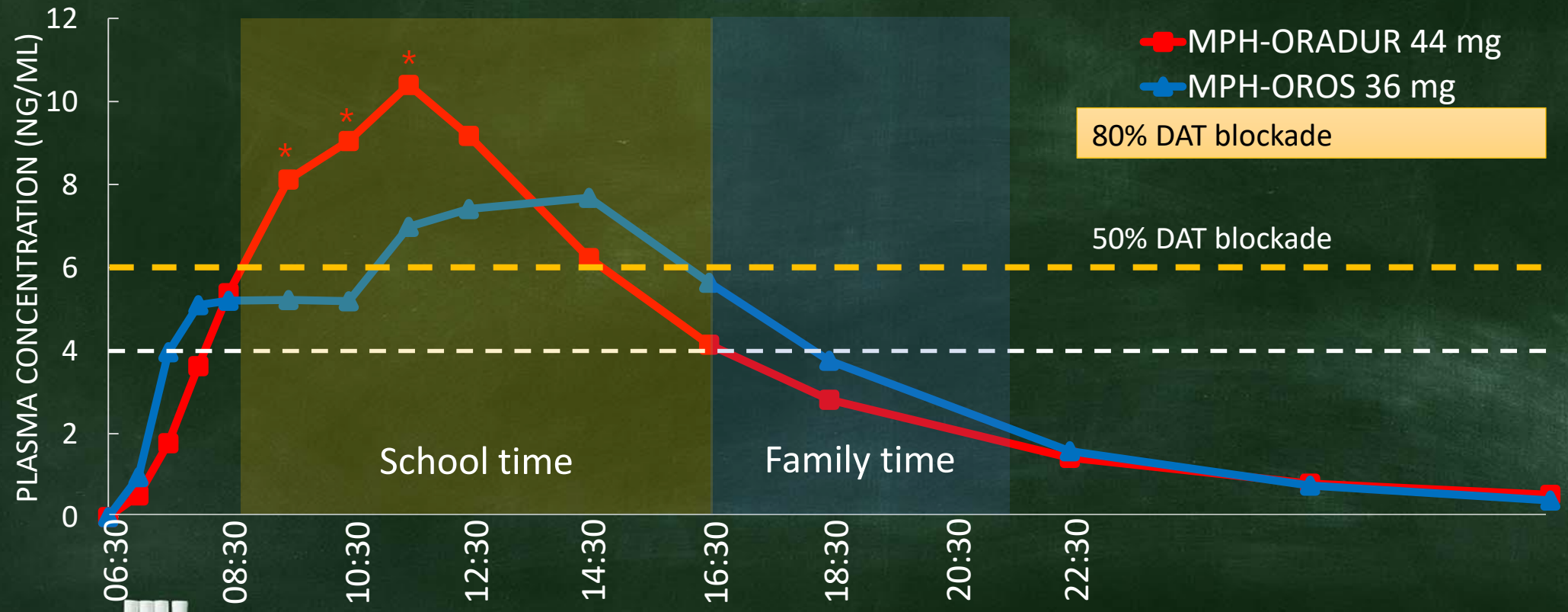
Evaluations
Plasma concentrations of methylphenidate
Main PK parameters: C_{max}, T_{max}, AUC_{0-t}, $AUC_{0-\infty}$, and $T_{1/2;}$ Safety: AEs

AE=adverse event; AUC0-∞=area under the concentration-time curve from time zero to infinity; AUC0-t=area under the concentration-time curve from time zero to time of the last quantifiable concentration; BMI=body mass index; T1/2=terminal elimination half-life; Orient Pharma. Clinical Study Report (Protocol No. PK NDA-T375-1206).

Methydur® SR Phase I Study:

Primary endpoint : pharmacokinetic profiles

Methydur® 44mg exhibited a **faster rate** and **higher extent of absorption** than Concerta® 36mg.



*: Significant difference presents between MPH-ORADUR 44 mg and MPH-OROS 36 mg. ($p<0.05$); Orient Pharma. Clinical Study Report (Protocol No. PK NDA-T375-1206).

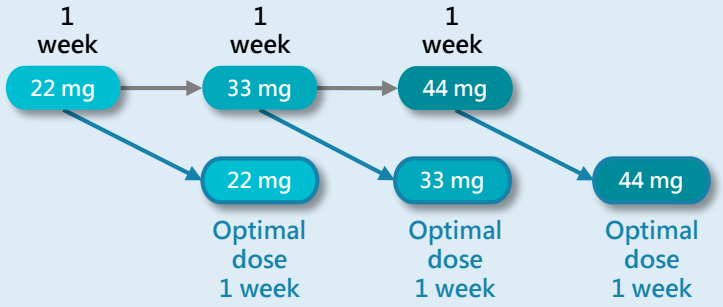
Methydur® SR Phase III Study:
OP-2PN012-301

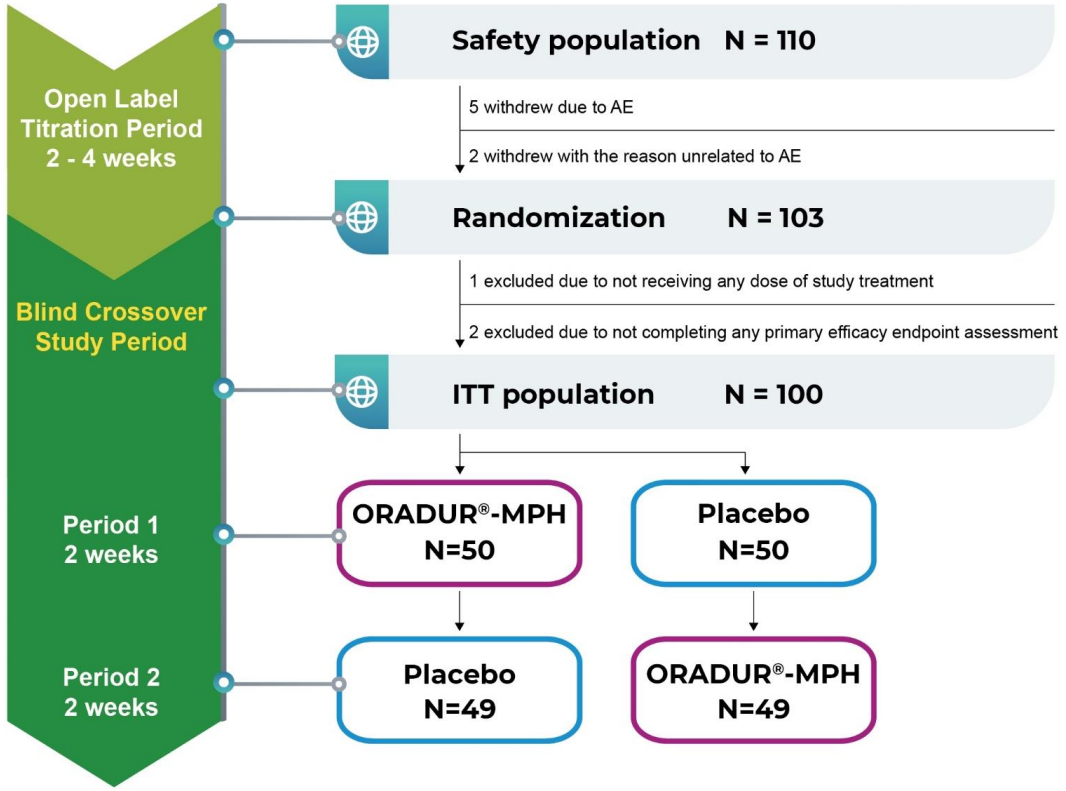
Phase III, Multi-Center, Randomized, Double-blind, Placebo Controlled, Two-way Cross-over clinical study to evaluate **safety** and **efficacy** of Methydur® in children and adolescents with ADHD.

Main inclusion criteria

- Age **6~18** years old
- Diagnosed with ADHD according to DSM-5 criteria within 1 year
- Could swallow study specific capsule (18 mm) without difficulty

Titration Period



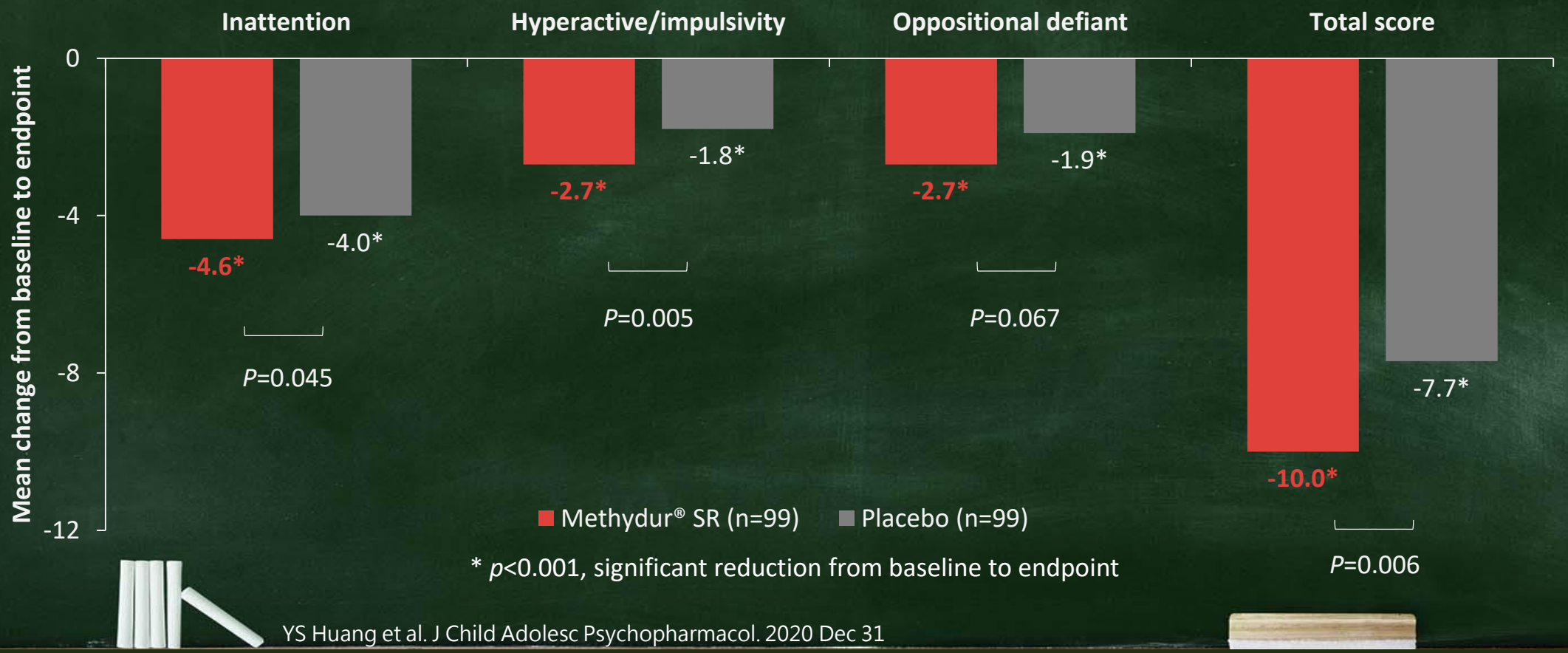


Methydur® SR was orally administered once daily in the morning within 20 minutes after breakfast. YS Huang et al. J Child Adolesc Psychopharmacol. 2020 Dec 31.

Methydur® SR Phase III Study:

SNAP-IV Teacher Form Score

The magnitude of **symptoms reduction from baseline to the endpoint was significantly greater for the ORADUR®-MPH group** than the placebo group.



YS Huang et al. J Child Adolesc Psychopharmacol. 2020 Dec 31

MPH Treatment Effectiveness in brain

fMRI analysis of brain regions

Treatment with **ORADUR®-MPH may increase the brain activity in the dACC , rDLPFC , and rIFG** corresponding to improving focused attention, sustained attention, and inhibition control, and decreasing impulsivity in drug naïve children with ADHD.

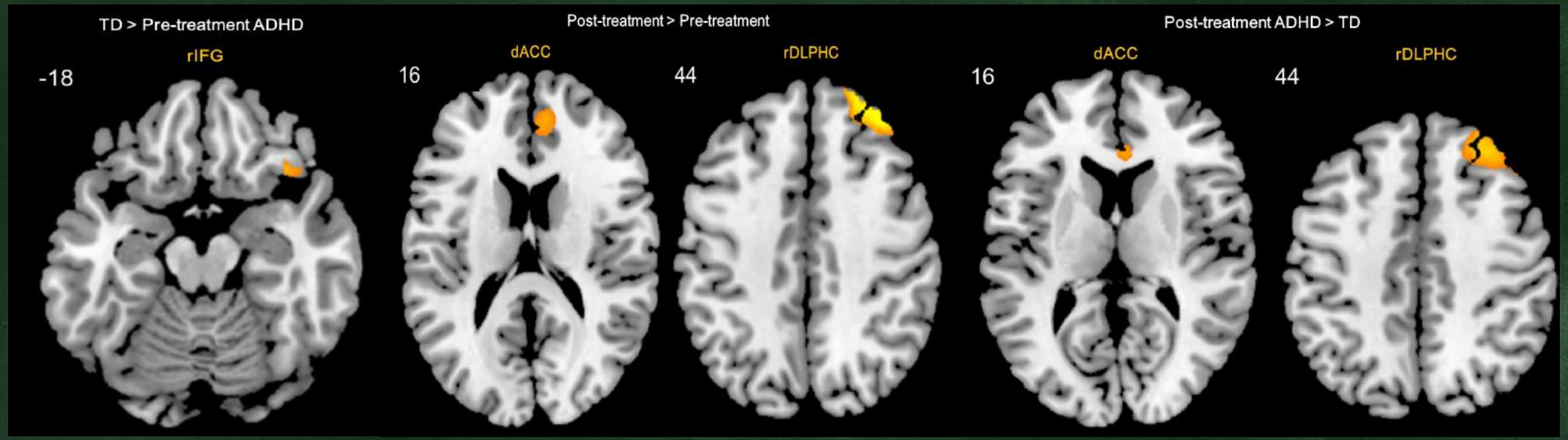


Fig. 2A Greater activation in the rIFG in TD.

Fig. 2B Greater activation in the dACC and the rDLPFC from pre to post treatment in ADHD.

Fig. 2C Greater activation in the dACC and the rDLPFC in post treatment ADHD than TD.

dACC: dorsal anterior cingulate cortex; rDLPFC: right dorsolateral prefrontal cortex;
rIFG: right inferior frontal gyrus
JCAP 2022 32:9 467-475

Non-head-to-head comparison

Safety profiles among different methylphenidate products

Methydur® had a better safety profile than Concerta® and Ritalin IR®.

Adverse Event	No. of patients with an AE (%)	
	Methydur®[1] ORADUR®-MPH (N=110)	Placebo (n=101)
Decreased appetite	53 (48.2%)	1 (1.0%)
Insomnia or trouble sleeping	22 (20.0%)	0 (0.0%)
Headache	9 (8.2%)	1 (1.0%)
Stomachache	5 (4.5%)	1 (1.0%)
Anxious mood	2 (1.8%)	0 (0.0%)
Tics	2 (1.8%)	0 (0.0%)

Adverse Event	No. of patients with an AE (%)	
	Concerta®[2] OROS®-MPH (n=32)	Ritalin®[2] IR-MPH (n=32)
Decreased appetite	15 (46.9%)	19 (59.4%)
Insomnia or trouble sleeping	13 (40.6%)	15 (46.9%)
Headache	7 (21.9%)	11 (34.4%)
Stomachache	10 (31.3%)	8 (25.0%)
Anxious mood	6 (18.7%)	10 (31.3%)
Tics	5 (7.8%)	6 (18.8%)

IR=immediate release; OROS=osmotic-controlled release oral delivery system.

1. YS Huang et al. J Child Adolesc Psychopharmacol. 2020 Dec 31
2. Gau SS, et al. J Child Adolesc Psychopharmacol. 2006;16(4):441-55.

Modified-release MPH Formulations

Taiwan FDA approved long acting MPH

Licensed MPH	Tablet		Capsules			
Brand name	Concerta® / MPH-OROS®		Ritalin LA / MPH-SODAS®		Methydur® SR / MPH-ORADUR®	
Formulation	22% IR / 78% ER		50% IR / 50% ER		18% IR / 82% ER	
Available doses	18, 27, 36, 54 mg		10, 20, 30, 40 mg		22, 33, 44 mg	
Dose range	IR	ER	IR	ER	IR	ER
18-22mg	4	14	10	10	4	18
27-33mg	6	21	15	15	6	27
36-44mg	8	28	20	20	8	36
Titration	18 mg weekly		10 mg weekly		11 mg weekly	

IR=immediate release; ER=extended release.
OROS=Osmotic-controlled Release Oral Delivery System; SODAS=Spheroidal Oral Drug Absorption System. Concerta Package Insert 1702; Ritalin LA Package Insert TWI-101018

Pharmacokinetic Properties of Modified-release MPH Formulations

The NICE committee agreed that **HCP should be aware of the pharmacokinetic profiles** of ADHD medication because preparations can vary in their profiles[6].

Pharmacokinetic Profiles	Conc-Time Curve Pattern	$T_{max\ 1\&2}$ (hour)	$C_{max\ 1\&2}$ (ng/ml)	Duration (hour)[5]	Half-life (hour)	Maximized efficacy period*
MPH-IR[2] 10mg BID	First-order	1st : 1.8 2nd : 5.6	1st : 10.2 2nd : 15.3	4	2.5	08:20-10:30-14:30
MPH-OROS®[1] 18mg QD	First-order (Bi-modal)	6.8	3.7	10-12	3.5	13:30-18:30
MPH-SODAS®[2] 20mg QD	First-order (Bi-modal)	1st : 2 2nd : 6.6	1st: 10.3 2nd: 10.2	6-8	2.4	08:30-14:30
MPH-ORADUR®[3] 22mg QD	Near zero-order kinetic	3-5	7.1	8-12[4]	7.4	09:30-18:30

*Dose administered at 6:30am & 4 hours apart, time of major effective period stated from first Tmax to the end of duration of each dose. 1. MPH-OROS® Package insert Taiwan (Adult); 2.MPH-SODAS® Package insert Taiwan (Pediatric); 3. MPH-ORADUR® Package Insert Taiwan (Adult); 4. Data on file; 5. Expert Opin. Drug Metab. Toxicol. (2013) 9(8):1001-1014. 6. NICE guideline 2018

Methydur® SR

2019 Bio Asia-Taiwan : Innovation of the Year

Bio Asia = 台灣生物產業發展協會舉辦之亞洲生技大會

Take Home Messages

Features	Advantageous	Benefits
Near zero-order kinetic PK profile	Timely, 2 hours up to 6 ng/ml effective concentration that meet the needs of prime learning time	Experience efficacy in the morning to reduce anxiety about not being able to keep up
ORADUR® sustained release formulation	Adequate, 8-12 hours of action time, covering the needs of daily study and life	From class to self-study can be consistent
	Sleep well and strengthen the learning results of classes the next day	Spirit full in the next morning, increasing parents' confidence in continuous treatment.
Abuse-resistant	To prevent people intend to grind and smoke powder, to prevent the problem of drug abuse	Reduce the administrative burden and risk of misuse of controlled substances in school management
Size 4# capsule	Generally available in the smallest size capsules, HPMC is available for vegetarian use	School children with different swallowing abilities are easy to swallow and strengthen drug compliance

ONCE-DAILY
METHYDUR
methylphenidate sustained release capsule

International first launched, with fast onset and sustained-release characteristics, improve patients' compliance.

orientPHARMA
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