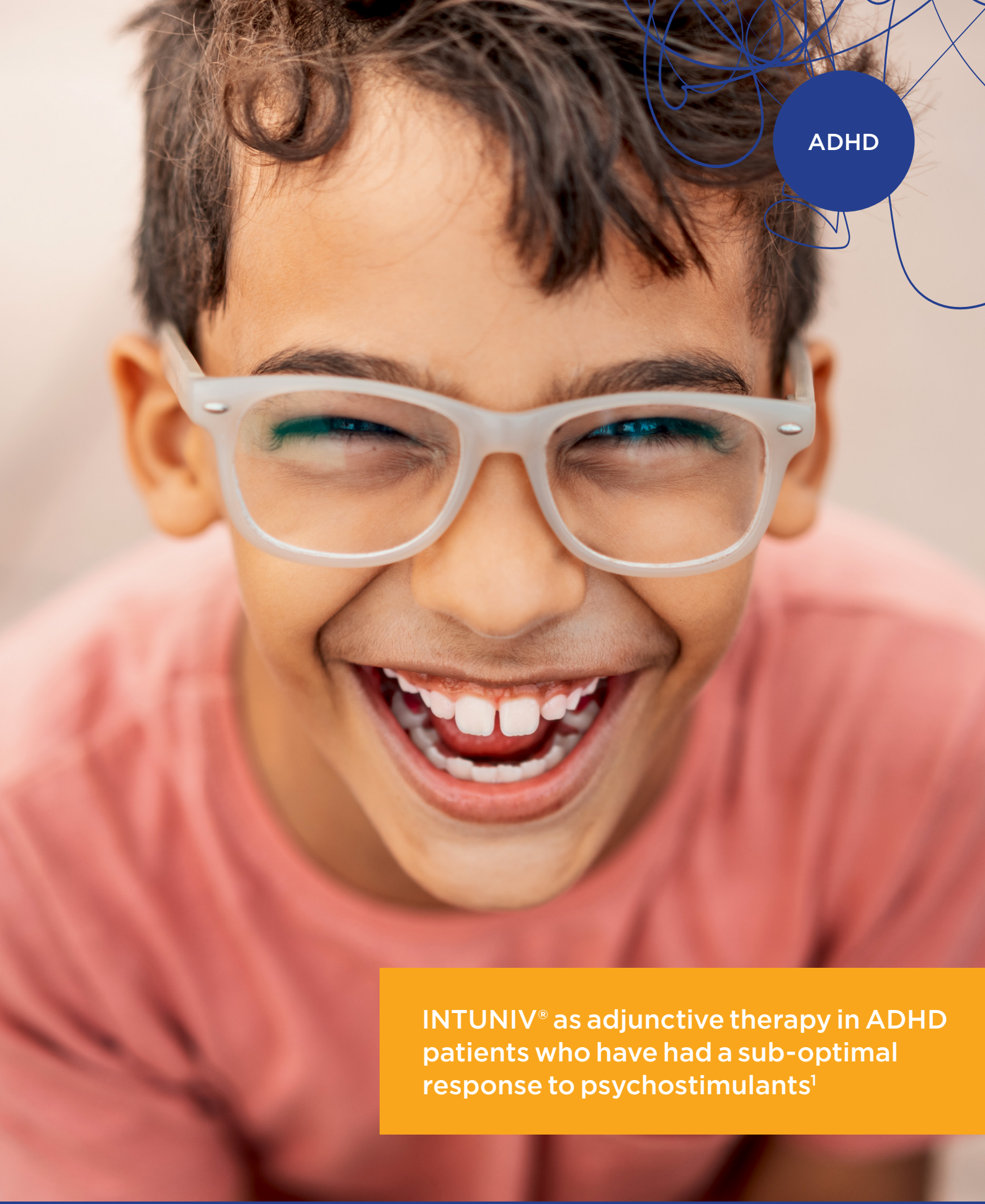

INTUNIV® as adjunctive therapy in ADHD patients who have had a sub-optimal response to psychostimulants[1]

ADHD, attention deficit hyperactivity disorder.

intuniv®
(guanfacine hydrochloride)
Modified Release Tablets 1•2•3•4 mg

Dylan*

Age: **8**
Weight: **33 kg**
Blood pressure: **105/70 mm/Hg**
Heart rate: **75 bpm regular**

Initial diagnosis and treatment

- **Diagnosis:** ADHD combined type. Baseline ADHD-RS-IV score: 37. CGI-S score 3.9.
- **Teacher report:** Struggles to focus in class, distracts others, constantly fidgets and calls out during class, spends most lunch times alone as other children find that his impulsiveness can make interactions challenging.
- **Parent report:** Does not listen, fights with older sister, has trouble organising himself for school, "a constant whirlwind".
- **Treatment history:** Short-acting methylphenidate 5 mg bd for 7 days; thereafter dose increased to 10 mg bd. After 2 months, Dylan was switched to long-acting methylphenidate as short-acting formulation was not providing adequate cover over the day. Started with 18 mg/day. Over the next 4 months titrated up to 54 mg/day. Dylan has remained on this dose for 6 weeks.

INTUNIV is indicated for the treatment of ADHD in children and adolescents 6-17 years old, as monotherapy (when stimulants or atomoxetine are not suitable, not tolerated or have been shown to be ineffective) or as adjunctive therapy to psychostimulants (where there has been a sub-optimal response to psychostimulants). INTUNIV must be used as part of a comprehensive ADHD management programme, typically including psychological, educational and social measures.[1]

*Hypothetical patient scenario.

ADHD, attention deficit hyperactivity disorder; **ADHD-RS-IV**, ADHD Rating Scale Version IV; **bd**, twice daily; **CGI-S**, Clinical Global Impression-Severity.

Recent presentation

- Dylan has been treated with long-acting methylphenidate 54 mg/day for 6 weeks.
- Many of Dylan's symptoms while at school have resolved and his focus has improved.
- **ADHD-RS-IV score:** 26. CGI-S score 3.7.
- **Parent report:** Still impulsive in the mornings and evenings. Continues to argue with his sister and his functioning remains affected by his ADHD when at home. Mother reports he has reduced appetite and some insomnia.

Dylan's recent presentation warrants a diagnosis of ADHD with sub-optimal response to psychostimulants[2]

Clinical trial definition of sub-optimal response to psychostimulants[2]

In the 9-week double-blind, placebo-controlled, dose-optimisation study conducted in paediatric patients (aged 6-17 years) with a diagnosis of ADHD, sub-optimal response was defined as:[2]

- ✓ ≥4 weeks stable dose of a long-acting psychostimulant with improvement but continued mild-to-moderate ADHD symptoms.
- ✓ ADHD-RS-IV total score ≥24.
- ✓ CGI-S score indicative of at least mild impairment ≥3.
- ✓ Investigator assessment of inadequate response to current psychostimulant.

ADHD, attention deficit hyperactivity disorder; **ADHD-RS-IV**, ADHD Rating Scale Version IV; **CGI-S**, Clinical Global Impression-Severity.

Efficacy, safety and tolerability trial of INTUNIV adjunctive to a long-acting psychostimulant for treatment of ADHD patients[1,2]

Wilens TE et al. J Am Acad Child Adolesc Psychiatry 2012;51:74-85.

Design[2]

Multicentre, 9-week, double-blind, placebo controlled, dose-optimisation, co-administration study conducted in paediatric patients (aged 6-17 inclusive) with a diagnosis of ADHD and a sub-optimal response to stimulants (n=455). The safety and efficacy of INTUNIV (1-4 mg/day) were evaluated when co-administered with psychostimulants (longer-acting formulations of mixed salts of a single-entity amphetamine product, lisdexamfetamine dimesilate, methylphenidate HCl, and dexmethylphenidate HCl). Patients continued to take their psychostimulant in the morning and were dosed either in the morning or the evening with INTUNIV (1-4 mg/day) or with placebo in addition to their psychostimulant. The majority of subjects reached optimal doses in the 0.05-0.12 mg/kg/day range. Symptoms of ADHD were evaluated as the change from baseline to endpoint (week 8 LOCF) in ADHD-RS-IV total scores.

Primary endpoint description[2]

- Change from baseline to endpoint (week 8 LOCF) in ADHD Rating Scale (ADHD-RS-IV) total scores.
- ADHD-RS-IV was administered by clinicians at all study visits through dose tapering.

Secondary endpoint description[2]

- CGI-S scale was performed at baseline and at each visit through dose tapering.
- CGI-I scale was also performed at all post baseline visits through dose tapering.

Safety[2]

No new safety signals were reported with INTUNIV as adjunctive therapy vs psychostimulants alone. The most common TEAEs (>10%) in the INTUNIV treatment groups were headache (21.2%) and somnolence (13.6%). Majority of TEAEs were mild or moderate in intensity. No deaths were reported during this study. Serious AEs occurred in three subjects (1%): all subjects were receiving INTUNIV + a psychostimulant, and all three events were considered unrelated to study medication by investigators.

Study results provide reasons to consider INTUNIV® as adjunctive therapy for eligible ADHD patients with a sub-optimal response to stimulants[1,2]

ADHD-RS-IV primary endpoint outcome: Patients treated with INTUNIV + psychostimulant had significantly greater improvement in ADHD symptoms vs those on placebo + psychostimulant:[1,2]

- **28% greater symptom improvement with morning dosing** (mean change from baseline -20.3 vs -16 placebo + stimulant, p=0.002)[2]
- **31% greater symptom improvement with evening dosing** (mean change from baseline -20.9 vs -16 placebo + stimulant, p<0.001)[2]

Clinical evidence supports the use of INTUNIV® as adjunctive therapy in ADHD patients with sub-optimal response to a psychostimulant[1,2]

ADHD, attention deficit hyperactivity disorder; **ADHD-RS-IV**, ADHD Rating Scale Version IV; **AE**, adverse event; **CGI-S**, Clinical Global Impression-Severity; **CGI-I**, Clinical Global Impression-Improvement; **LOCF**, last observation carried forward; **TEAE**, treatment-emergent adverse event.

Response time with INTUNIV® as adjunctive therapy in ADHD patients with sub-optimal response to a psychostimulant[2]

Patients treated with INTUNIV + psychostimulant showed significant improvements on ADHD-RS-IV total score (p<0.05) after:[2]

3 weeks of morning dosing (visit 5) and 5 weeks of morning dosing (visit 7) through endpoint.[2]

2 weeks of evening dosing (visit 4) through endpoint.[2]

How to start INTUNIV® as adjunctive therapy[1]

Start with 1 mg once daily and titrate gradually based on clinical response and tolerability[1]

- Recommended maintenance dose for INTUNIV as adjunctive therapy to a psychostimulant is within the range of 1-4 mg/day, depending on clinical response and tolerability.[1]
- Doses above 4 mg/day have not been evaluated in adjunctive therapy studies.[1]
- Weight-based recommended target dose ranges are available to assist in clinical decision making.[1]
  - In the dose-optimisation study: Majority of patients reached optimal doses in the 0.05-0.12 mg/kg/day range.[2]

Titrate

1 mg at a time, with 1 week or more between dose changes

Tablets not actual size or colour.

Dose and administration[1]

✓ **Starting dose:** 1 mg once daily swallowed whole.

✓ **Titrate gradually:** Increments of no more than 1 mg per week.

✓ **Maintenance dose:** 0.05-0.12 mg/kg/day.

For further details on Dosage and Administration, please refer to the Approved Product Information.

INTUNIV®: Important safety information[1]

Rebound Effects: Blood pressure and heart rate increase upon discontinuation or treatment interruption[1]

- Blood pressure and pulse may increase following discontinuation of INTUNIV.
- In post-marketing experience, hypertensive encephalopathy has been very rarely reported upon abrupt discontinuation of INTUNIV.
- Caution is recommended in children who have gastrointestinal illnesses that lead to vomiting because the resulting inability to take medications may lead to a risk of guanfacine rebound effects.
- To minimise the risk of an increase in blood pressure upon discontinuation, the total daily dose of INTUNIV should be tapered in decrements of no more than 1 mg every 3-7 days.
- Blood pressure and pulse should be monitored when reducing the dose or discontinuing INTUNIV.

Syncope, hypotension, bradycardia[1]

- Measure heart rate and blood pressure prior to initiating therapy, following dose adjustments, periodically during treatment and following drug discontinuation.
- Observe caution if using INTUNIV in patients who have a history of hypotension, heart block, bradycardia, or other cardiovascular disease.
- Caution is advised when treating patients with INTUNIV who have a history of syncope or a condition that may predispose them to syncope, such as hypotension, orthostatic hypotension, bradycardia, or dehydration.
- Caution is advised when treating patients with INTUNIV who are being treated concomitantly with anti-hypertensives or other drugs that reduce blood pressure or heart rate, QT prolonging drugs, and drugs that increase the risk of syncope.

Aggression[1]

- Aggressive behaviour or hostility is often observed in children and adolescents with ADHD and has been reported in clinical trials and in the post-marketing experience of some medications indicated for the treatment of ADHD. Although there is no systematic evidence that guanfacine causes aggressive behaviour or hostility, patients beginning treatment of ADHD should be monitored for the appearance of, or worsening of, aggressive behaviour or hostility.

Sedation and somnolence[1]

- INTUNIV may cause somnolence and sedation.
- Before INTUNIV is used with other centrally active depressants, the potential for additive sedative effects should be considered.
- Caution patients against operating heavy equipment or driving until they know how they respond to treatment with INTUNIV.
- Patients should avoid use with alcohol.

Suicidal ideation[1]

- There have been post-marketing reports of suicide-related events in patients treated with ADHD drugs, including cases of ideation, attempts, and very rarely, completed suicide.
- The mechanism of this risk is not known. ADHD and its related co-morbidities may be associated with increased risk of suicidal ideation and/or behaviour. Therefore, it is recommended for patients treated with ADHD drugs that caregivers and physicians monitor for signs of suicide-related behaviour, including at dose initiation/optimisation and drug discontinuation.
- Patients should be encouraged to report any distressing thoughts or feelings at any time to their healthcare professional.

INTUNIV®: Important safety information[1]

Effects on height, weight and BMI[1]

- Children and adolescents treated with INTUNIV may show an increase in their BMI.
- Monitoring of height, weight and BMI should be done prior to initiation of therapy and then every 3 months for the first year, taking into consideration clinical judgement.
- 6-monthly monitoring should follow thereafter, with more frequent monitoring following any dose adjustment.

BMI, body mass index.

For further details on Safety, please refer to the Approved Product Information.

Please review Product Information before prescribing. Product Information is available from Takeda Pharmaceuticals Australia Pty Ltd. Phone: 1800 012 612. Email: medinfoAPAC@takeda.com

For further information about the appropriate selection of patients and prescribing of INTUNIV, please visit http://www.intunivguide.com/au (password: onetakeda)

PBS Information: Authority required (Streamlined). Attention deficit hyperactivity disorder (ADHD); patient must be or have been diagnosed between the ages of 6 and 17 years inclusive. EITHER as monotherapy in patients who are contraindicated or intolerant to stimulants; OR as adjunctive therapy with a maximum tolerated dose of stimulant, in patients experiencing residual moderate to severe ADHD symptoms.

Minimum Product Information INTUNIV® (guanfacine hydrochloride). Indication: INTUNIV is indicated for the treatment of attention deficit hyperactivity disorder (ADHD) in children and adolescents 6-17 years old, as monotherapy (when stimulants or atomoxetine are not suitable, not tolerated or have been shown to be ineffective) or as adjunctive therapy to psychostimulants (where there has been a sub-optimal response to psychostimulants). INTUNIV must be used as part of a comprehensive ADHD management programme, typically including psychological, educational and social measures. **Dosage and Administration:** Once daily either morning or evening. The modified-release tablet should not be crushed, chewed, or broken before swallowing. Recommended starting dose is 1mg for both monotherapy and when co-administered with psychostimulants. Dose adjustments in increments of no more than 1 mg/week. **Contraindications:** History of hypersensitivity to INTUNIV, its excipients, or other products containing guanfacine. **Precautions:** Syncope, hypotension, bradycardia; dizziness, aggression, sedation, fatigue and somnolence; suicidal ideation; effects on height, weight and body mass index; Rebound effects (Blood pressure and heart rate increase) upon discontinuation or treatment interruption (in postmarketing experience, hypertensive encephalopathy has been very rarely reported upon abrupt discontinuation). Caution in pregnancy (B3), breastfeeding and while driving or using machines. Safety and efficacy not studied in patients under 6 years of age, adults and elderly. No data in paediatric patients 6 – 17 years old with hepatic impairment. Dose reduction in patients with severe renal impairment and end stage renal disease or requiring dialysis. **Interactions:** CYP3A4/5 inhibitors, CYP3A4 inducers, transporters, valproic acid, antihypertensive drugs. **Adverse Effects:** Very Common reactions: Somnolence, headache, abdominal pain, fatigue. Common reactions: decreased appetite, insomnia, anxiety, affect lability, middle insomnia, nightmare, depression, sedation, dizziness, lethargy, bradycardia, hypotension, orthostatic hypotension, asthma, nausea, vomiting, diarrhoea, dry mouth, constipation, abdominal/stomach discomfort, rash, enuresis, irritability, blood pressure decreased, weight increased. (pi-00686. V5.0)

References: 1. INTUNIV® (guanfacine hydrochloride) Approved Product Information. **2.** Wilens TE *et al. J Am Acad Child Adolesc Psychiatry* 2012; 51:74-85. **3.** Australian Register of Therapeutic Goods. Available at: www.tga.gov.au/artg

Takeda Pharmaceuticals Australia Pty Ltd, Sydney, NSW 2000.
Tel: 1800 012 612. Email: medinfoAPAC@takeda.com ABN 71 095 610 870.

Date of Preparation September 2022. C-APROM/AU/INTU/0004. Z22_1787