

5.20 GLYCOMACROPEPTIDE AND ESSENTIAL AMINO ACIDS WITH VITAMINS AND MINERALS

Sachets containing oral powder 31 g, 30, Tylactin Build 20®, Cortex Health Pty Ltd

1 Purpose of application

- 1.1 The minor submission sought listing of a new glycomacropeptide (GMP) formula, Tylactin Build 20® (herein referred to as Tylactin Build), for the dietary management of tyrosinaemia.

Table 1: Key components of the clinical issue addressed by the submission (as stated in the submission)

Component	Description
Population	Tyrosinaemia
Intervention	Tylactin Build, containing 20 g protein equivalent per serve
Comparator	Tylactin® RTD 15
Outcomes	Improved blood phenylalanine control, leading to improvements in cognitive outcomes, normal physical growth and quality of life.
Clinical claim	In children and adults with tyrosinaemia Tylactin Build is as effective as Tylactin RTD 15 at improving tyrosine & phenylalanine control, leading to similar benefits at maintaining desired long term clinical outcomes.

Source: Table 1.1.1, p4 of the submission.

2 Background

Registration status

- 2.1 Tylactin Build does not require registration with the Therapeutic Goods Administration. The sponsor confirmed it meets the requirements to be classified as a “Food for Special Medical Purpose” (FSMP) regulated under *The Australia New Zealand Food Standards Code – Standard 2.9.5: Food for Special Medical Purposes*.

Previous PBAC consideration

- 2.2 Tylactin Build has not previously been considered by the PBAC.
- 2.3 The sponsor made a previous submission to the PBAC in April 2019. The submission was subsequently withdrawn after advice was sought from the Nutritional Products Working Party (NPWP) prior to consideration by the PBAC.
- 2.4 The NPWP had previously noted the requested listing of Tylactin Build as an alternative to other GMP formulas listed on the PBS for the dietary management of tyrosinaemia, including Tylactin® RTD 15 and Tylactin Complete® (NPWP Minutes, May 2019).
- 2.5 Matters of concern raised by the NPWP are outlined in Table 2.

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Table 2: NPWP matters of concern in previous consideration (May 2019)

Matters of concern	How the resubmission addresses it
The NPWP noted the product was lower in calories than the current alternatives but considered the vitamin and mineral content of the formulation per the provided product data cards was very low. The NPWP advised the product appeared to be nutritionally incomplete. (Paragraph 5.1)	The Sponsor reformulated the product to include higher levels of vitamins and minerals (see Table 3).
The NPWP noted the levels of vitamin B12 and iron were at sub-nutritional levels and requirements for these nutrients were difficult to meet on highly restricted diets. (Paragraph 5.1)	The levels of vitamin B12 in the previous formulation of the product were increased in this formulation, from 0.2mg to 0.9mg. The iron levels were also increased from 1.5mg to 7.2mg.

Source: Compiled during the evaluation. Paragraph references refer to the May 2019 Tylactin Build 20 Minor Overview.

3 Requested listing

- 3.1 The submission requested a Restricted Benefit listing of Tylactin Build aligned with existing listings for nutritional products for tyrosinaemia.

Medicinal Product Pack (Name, form & strength and pack size)	PBS item code	Max. qty packs	Max. qty units	No. of Rpts	Available brands
GLYCOMACROPEPTIDE AND ESSENTIAL AMINO ACIDS WITH VITAMINS AND MINERALS glycomacropeptide and essential amino acids with vitamins and minerals containing powder for oral liquid, 30 x 31 g sachets	NEW	4	4	5	Tylactin Build 20

Category / Program: GENERAL – General Schedule (Code GE)
Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners <input checked="" type="checkbox"/> Nurse practitioners
Restriction type: <input checked="" type="checkbox"/> Restricted benefit
Indication: Tyrosinaemia

For more detail on PBAC’s view, see section 7 PBAC outcome.

4 Comparator

- 4.1 The submission nominated Tylactin RTD 15 as the most appropriate comparator, being the most used GMP formulation for tyrosinaemia. The NPWP previously considered that this was appropriate (NPWP Minutes, May 2019).
- 4.2 Tylactin RTD 15 (a GMP formula) was recommended on a cost-minimisation basis against TYR Cooler® 20 and TYR Cooler® 15 (amino acid formulas) on an equivalent price per gram of protein equivalent (PE) basis (para 6.1, Tylactin RTD 15 Public Summary Document (PSD), July 2015).
- 4.3 In recommending TYR Sphere 20® for PBS listing, the PBAC recommended listing on a cost minimisation basis to the lowest cost alternative GMP formula listed on the PBS for the same condition, at an equivalent cost per gram of PE (para 6.1, TYR Sphere 20 PSD, July 2019).

- 4.4 In recommending Tylactin Complete® for PBS listing, the PBAC recommended listing on a cost minimisation basis to Tylactin RTD 15 at an equivalent cost per gram of PE (para 6.1, Tylactin Complete PSD, November 2017).
- 4.5 As at 1 July 2020, Tylactin RTD 15 had a price per gram of PE of \$1.64; TYR Cooler 15 and TYR Cooler 20 were priced at \$1.33 per gram of PE, due to being subject to a 5% statutory price reduction on 1 April 2016.
- 4.6 A consideration for PBAC is that, under Section 101(3B) of the *National Health Act 1953*, when the proposed medicine is substantially more costly than an alternative therapy, the committee cannot make a positive recommendation unless it is satisfied that, for some patients, the proposed medicine provides a significant improvement in efficacy and/or reduction of toxicity over the alternative therapy. In this case, the alternative therapy is amino acid based formulas for treatment of tyrosinaemia. If the committee is so satisfied, it must make a statement to this effect.

For more detail on PBAC's view, see section 7 PBAC outcome.

5 Consideration of evidence

Sponsor hearing

- 5.1 There was no hearing for this item as it was a minor submission.

Consumer comments

- 5.2 The PBAC noted that no consumer comments were received for this item.

Clinical trials

- 5.3 The minor submission was based on the same clinical evidence presented for earlier glycomacropeptide formulations. This was valid and transposable to Tylactin Build.

Other clinical matters

- 5.4 The submission argued that Tylactin Build provided an important clinical alternative for patients with tyrosinaemia who ordinarily require strict, lifelong dietary therapy.
- 5.5 The submission argued that Tylactin Build offered a clinical advantage over alternatives, as it is a low energy formulation of natural GMP that provided the same amount of PE content per day as Tylactin RTD 15 using fewer sachets/serves per day. The submission stated that this was advantageous to some patients as it could support weight loss or the maintenance of healthy weight compared to alternatives, and would be suitable for patients with Type 2 Diabetes.
- 5.6 The submission argued Tylactin Build, being a whole protein supplement, has improved palatability and satiety versus amino acid formulas. The submission stated that the higher large neutral amino acid (LNAA) content of GMP may inhibit phenylalanine transport across the blood brain barrier and intestinal mucosa, providing further benefits over synthetic amino acid formulas including improving

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cognitive outcomes. The submission also stated that the formula contains probiotics to aid digestive health.

- 5.7 The submission noted that in May 2019 the NPWP did not support the listing of Tylactin Build due to the levels of iron and vitamin B12, and that the sponsor had reformulated the product to have a much higher nutrient content. This is outlined in Table 3.

Table 3: Nutrient comparison of Tylactin Build (former and current), Tylactin RTD 15 and TYR express 20.

Nutritional Information	Tylactin Build 20 Per 31 g sachet Current submission	Tylactin Build 20 Per 28 g sachet 2019 submission	Tylactin RTD 15 Per 250 mL tetra pack Comparator	TYR express 20 Per 34 g sachet Comparator ^a
Energy, protein, carbohydrate, fat, fibre:				
Energy (kJ)	419	418	837	429
Protein (g)	20	20	15	20
Carbohydrate (g)	0.7	3.5	23	4.7
Fat (g), total	1.3	1.5	5.0	0.07
Saturated fat (g)	0.3	0.1	2.0	0
DHA	50	-	-	-
Fibre (g)	0.4	0	1.0	-
Vitamins:				
Vitamin A, RAE (mcg)	326	65	270	283
Vitamin C (mg)	53	8.1	28	36.7
Vitamin D (mcg)	15	2.9	6.3	4.5
Vitamin E (mg)	6.0	1.1	4.5	5.3
Vitamin K1 (mcg)	18	3.6	30	34
Vitamin K2 (mcg)	18	3.6	0	-
Thiamine (mg)	0.5	0.1	0.4	0.68
Riboflavin (mg)	0.5	0.1	0.4	0.78
Niacin (mg)	11	1.2	5.0	8.4
Vitamin B6 (mg)	0.5	0.1	0.4	1.0
Folic acid (mcg) DFE	120	14	140	136
(Folic acid mcg)	71	-	-	-
Vitamin B12 (mcg)	0.9	0.2	0.8	1.6
Pantothenic acid (mg)	2.2	0.4	1.8	2.7
Biotin (mcg)	9.6	1.9	8	63.9
Choline (mg)	30	40	206	
Minerals, trace elements:				
Calcium (mg)	459	119	350	407
Chromium (mcg)	16	3.1	13	29.9
Copper (mg)	0.2	0.0	0.2	0.75
Iodine (mcg)	69	14	57	85.7
Iron (mg)	7.2	1.5	4.5	7.3
Magnesium (mg)	94	28	120	128
Manganese (mg)	1.0	0.2	0.8	1.1
Molybdenum (mcg)	18	3.6	15	49
Phosphorous (mg)	517	150	315	363
Selenium (mcg)	24	4.8	20	29.9
Zinc (mg)	4.5	0.9	3.3	7.3
Potassium (mg)	770	365	340	320

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Nutritional Information	Tylactin Build 20 Per 31 g sachet Current submission	Tylactin Build 20 Per 28 g sachet 2019 submission	Tylactin RTD 15 Per 250 mL tetra pack Comparator	TYR express 20 Per 34 g sachet Comparator ^a
Sodium (mg)	203	202	300	173
Chloride (mg)	120	22	162	248
Amino Acids:				
L-alanine (mg)	875	660	700	144
L-arginine (mg)	2040	2030	1593	1850
L-aspartic acid (mg)	1247	940	1000	2860
L-cysteine (mg)	13	10	162	690
L-glutamic acid (mg)	2732	2060	2250	1830
Glycine (mg)	1939	1900	148	1500
L-histidine (mg)	483	480	361	1010
L-isoleucine (mg)	1499	1130	1300	1680
L-leucine (mg)	3678	3600	3000	2690
L-lysine (mg)	1415	1200	818	1910
L-methionine (mg)	292	220	180	430
L-phenylalanine (mg)	28	28	25	-
L-proline (mg)	1698	1280	1400	1550
L-serine (mg)	1074	810	800	1180
L-aurine (mg)	0	0	30	45
L-threonine (mg)	2427	1830	2200	1290
L-tryptophan (mg)	283	280	219	540
L-tyrosine (mg)	3.0	3.0	3.0	-
L-valine (mg)	1207	910	900	1830

Source: April 2019 submission table 1.4.4 and April 2020 submission table 1.4.4.

^a Compiled from the product information on the Nestlé Health Science website.

Bold: indicates significant changes to the formulation since the April 2019 submission.

Nutritional product cost/patient/year: \$49,057.32

5.8 The above calculation of nutritional product cost per patient per year was derived from the DPMQ for one month’s supply (\$4,088.11¹) over 12 months, and assumed that a patient would receive the maximum quantity (4 packs) per dispensing, however this may not occur in practice due to variations in individual patient needs.

Estimated PBS usage & financial implications

5.9 The submission derived a requested price based on a cost minimisation with the nominated comparator (Tylactin RTD 15) at the same price per gram of PE of \$1.64² at the approved ex-manufacturer price (AEMP).

5.10 The submission argued that Tylactin Build would only substitute for alternative GMP formulations for tyrosinaemia, which are listed at a price per gram of PE of \$1.64.

¹ The DPMQ presented in the submission was incorrectly calculated to be \$4297.95 due to incorrect application of the wholesaler mark-up per pack.

² Based on the 1 May 2020 PBS schedule, Tylactin RTD has an AEMP of \$738.00 per pack of 30 cartons each containing 15 g of protein equivalent (PE). Tylactin Build provides 30 sachets, each containing 20 g of PE at a requested AEMP of \$984.00. Both give a resultant price per gram of PE for \$1.64 at the AEMP.

5.11 The submission claimed it was difficult to estimate the number of patients based on PBS utilisation data, as prescription data is an unreliable measure of patients due to variation in individual patient needs and use. The submission therefore provided estimates of prescriptions over six years, as outlined in Table 4.

Table 4: Estimated PBS utilisation and financial estimates

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Tylactin Build 20 scripts						
Cost at DPMQ (\$4,088.11 ^a)	\$	\$	\$	\$	\$	\$
Minus Co-pays (average \$18.67)	-\$	-\$	-\$	-\$	-\$	-\$
Net cost to PBS/RPBS	\$	\$	\$	\$	\$	\$

Source: Tylactin Build Financial Analyses spreadsheet (submission – Scripts - PBS). Costs rounded to nearest whole dollar amount.

^a Secretariat calculated DPMQ

Italics: calculated during evaluation

The redacted table shows that at Year 6, the estimated number of scripts was less than 10,000 and the net cost to the PBS/RPBS would be less than \$10 million.

5.12 The minor submission estimated no financial implications to the PBS/changes in PBS usage as the submission expected Tylactin Build only to substitute for alternative GMP products for tyrosinaemia. The submission argued the net cost to the PBS would likely be zero, as an equivalent amount of PE would be replaced from the comparators. As Tylactin Build contains more PE per sachet than Tylactin RTD 15 but the same number of serves per maximum quantity, if these packs were consumed at the same rate there may be a cost to the PBS.

5.13 If the PBAC considers amino acid formulas for tyrosinaemia as appropriate comparators, this will result in a net saving to the PBS.

For more detail on PBAC’s view, see section 7 PBAC outcome.

6 NPWP Consideration

6.1 The NPWP recalled its May 2019 consideration that the vitamin and mineral content of the formulation, in particular vitamin B12 and iron levels, was very low. The NPWP noted that the sponsor had since reformulated the product and increased the levels of vitamin B12 and iron, as well as adding docosahexaenoic acid (DHA). The NPWP considered that the new formulation was nutritionally complete.

6.2 The NPWP noted that the requested price was \$1.64 per gram of PE, and that this was the same price as other GMP formulas listed on the PBS for tyrosinaemia. The NPWP noted that this was higher than that of the listed amino acid formulas for tyrosinaemia.

6.3 The NPWP supported the listing of Tylactin Build for the dietary management of tyrosinaemia and considered that the most appropriate comparator would be the lowest cost alternative GMP formula listed on the PBS for treatment of tyrosinaemia. However, the NPWP considered that GMP formulas were not superior in efficiency or safety to amino acid formulas in tyrosinaemia.

- 6.4 The NPWP noted that improved palatability of GMP versus free amino acids has not been formally studied in tyrosinaemia, so there is no clinical evidence to support the submission's claim.

For more detail on PBAC's view, see section 7 PBAC outcome.

7 PBAC Outcome

- 7.1 The PBAC recommended the Restricted Benefit listing of a new GMP formula, Tylactin Build, for the dietary management of tyrosinaemia on a cost minimisation basis to the lowest cost alternative on the PBS for the same condition, at an equivalent cost per gram of PE.
- 7.2 The PBAC recalled that Tylactin RTD 15 was recommended at the same price per gram of protein as TYR Cooler 20 and TYR Cooler 15. The PBAC agreed with the NPWP advice that GMP formulas were not superior in efficacy or safety to amino acid formulas for tyrosinaemia, and noted that the NPWP supported the listing of Tylactin Build.
- 7.3 The PBAC noted that, under Section 101(3B) of the *National Health Act 1953*, when the proposed medicine is substantially more costly than an alternative therapy, the committee cannot make a positive recommendation unless it is satisfied that, for some patients, the proposed medicine provides a significant improvement in efficacy and/or reduction of toxicity over the alternative therapy. The PBAC considered that TYR express 20, TYR Cooler 20 and other similar amino acid and GMP formulas for the treatment of tyrosinaemia were appropriate alternative therapies, and that Tylactin Build did not provide a significant improvement in efficacy or reduction of toxicity over these alternatives. The PBAC therefore advised that Tylactin Build should be cost-minimised to the lowest cost alternative for the treatment of tyrosinaemia.
- 7.4 The PBAC considered that Tylactin Build is suitable for inclusion in the PBS medicines for prescribing by nurse practitioners.
- 7.5 The PBAC advised that the Early Supply Rule should not apply to Tylactin Build.
- 7.6 The PBAC recommended under Section 101(3BA) of the *National Health Act 1953* that Tylactin Build should be treated as interchangeable on an individual patient basis with similar nutritional products for treatment of tyrosinaemia.
- 7.7 The PBAC noted that its recommendation was on a cost-minimisation basis and advised that, because Tylactin Build is not expected to provide a substantial and clinically relevant improvement in efficacy, or reduction of toxicity, over the lowest cost alternative for the treatment of tyrosinaemia, or not expected to address a high and urgent unmet clinical need given the presence of an alternative therapy, the criteria prescribed by the National Health (Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2009 for Pricing Pathway A were not met.
- 7.8 The PBAC noted that this submission is not eligible for an Independent Review since it received a positive recommendation.

Outcome:

Recommended

8 Recommended listing

8.1 Add new medicinal product:

Medicinal Product Pack (Name, form & strength and pack size)	PBS item code	Max. qty packs	Max. qty units	No. of Rpts	Available brands
GLYCOMACROPEPTIDE AND ESSENTIAL AMINO ACIDS WITH VITAMINS AND MINERALS glycomacropeptide and essential amino acids with vitamins and minerals containing powder for oral liquid, 30 x 31 g sachets	NEW	4	4	5	Tylactin Build 20

Restriction Summary 5533 / Treatment of Concept: 5533

Category / Program: GENERAL – General Schedule (Code GE)
Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners <input checked="" type="checkbox"/> Nurse practitioners
Restriction type: <input checked="" type="checkbox"/> Restricted benefit
Indication: Tyrosinaemia

This restriction may be subject to further review. Should there be any changes made to the restriction the Sponsor will be informed.

9 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised through the Pharmaceutical Benefits Scheme (PBS) in Australia. It considers applications regarding the listing of medicines on the PBS and provides advice about other matters relating to the operation of the PBS in this context. A PBAC decision in relation to PBS listings does not necessarily represent a final PBAC view about the merits of the medicine or the circumstances in which it should be made available through the PBS. The PBAC welcomes applications containing new information at any time.

10 Sponsor's Comment

The sponsor had no comment.