Post-Market Review of Products Used in the Management of Diabetes:

Stage 3 - Medicines Used in the Treatment of Type 2 Diabetes

Novo Nordisk Pharmaceuticals Pty Ltd

July 2013

Novo Nordisk Pharmaceuticals welcomes the opportunity to provide input to Stage 3 of the Post-Market Review of Products Used in the Management of Diabetes - Medicines Used in the Treatment of Type 2 Diabetes.

1. Background:

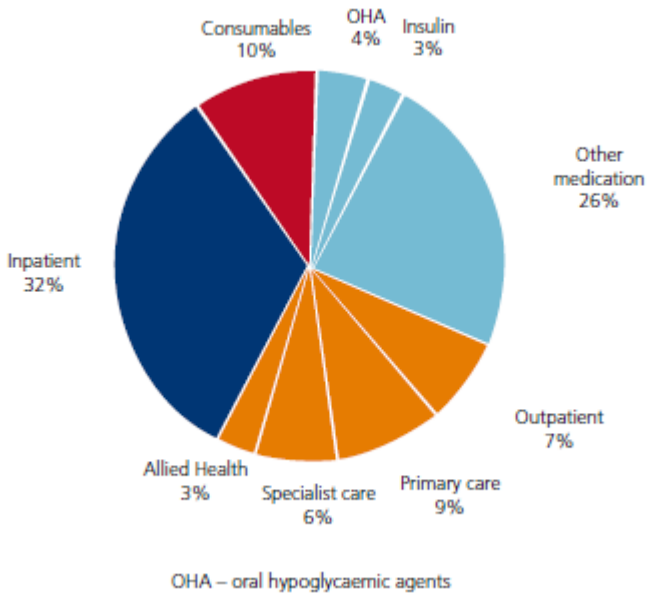
There are an estimated 1.5million people living with diabetes in Australia, including those who are undiagnosed, and type 2 diabetes contributes approximately 85% to this disease burden[1]. Diabetes is the fastest growing chronic disease in Australia and is predicted to become the leading burden of disease in the next 5 years[2].

Type 2 diabetes is a progressive disease which is characterised by progressive loss of beta-cell function and insulin production, coupled with increasing insulin resistance. The foundation for the treatment paradigm for type 2 diabetes is a healthy diet and exercise, coupled with a choice of oral hypoglycaemic agents and injectable therapies which target different biochemical pathways and which can be used optimally at different stages of the disease progression. The ultimate aim of diabetes management is to achieve optimal glycaemic control (target HbA_{1c}<7.0%) in order to decrease the risk of long term microvascular (retinopathy, neuropathy and nephropathy) and macrovascular complications, whilst minimising any side effects associated with the therapy as well as minimising the individual burden to the person of coping with a chronic and progressive disease. It is therefore imperative when reviewing the medicines used in the treatment of diabetes, that a holistic approach is taken which not only considers direct clinical outcomes, but also places equal consideration on important individual benefits such as reduced side effects, convenience and quality of life.

It is also important to note that a review of medicines used in the treatment of type 2 diabetes, is an extremely narrow focus when considering the impact of diabetes in the community. Diabetes is a National Health Priority Area and living with the long term complications of diabetes not only represents a significant health burden to the individual and their families but it is also a significant cost burden to the health system. Ironically, only 7% of the direct healthcare costs for people with type 2 diabetes are comprised of diabetes medications (Figure 1), with the presence of diabetes complications contributing more than double to the healthcare costs (Table 1). It would therefore seem more appropriate to ensure that in the immediate term, people with type 2 diabetes have access to the latest advances in diabetes therapy and technologies providing the most effective and patient centric treatments, so that in the long term, diabetes complications and the burden to the individual and the costs to the broader community of treating complications are reduced. This is in keeping with the recently released National Diabetes Strategy and Action Plan (Diabetes Australia 2013) which highlights *"Ensure access to treatments and technologies to support prevention of complications and burden"* as one of the key goals.

[1] Shaw et al., Diabetes: The silent pandemic and its impact on Australia 2012
[2] Diabetes Australia – National Diabetes Strategy and Action Plan 2013

Figure 1: Direct healthcare costs for people with type 2 diabetes



Reproduced from Shaw et al., Diabetes: The silent pandemic and its impact on Australia 2012; Based on data from Colagiuri *et al.,* DiabCost Australia 2003

Table 1: The average annual healthcare cost of type 2 diabetes per person[3]

	Type 2 diabetes
No complications of diabetes	$4,025
Microvascular complications only	$7,025
Macrovascular complications only	$9,055
Micro- and macrovascular complications	$9,645

2. General Comments to the Current Review of Medicines Used in the Treatment of Type 2 Diabetes.

Novo Nordisk agrees that it is both appropriate and responsible to undertake reviews regarding the Quality Use of Medicines in Australia, however has serious concerns regarding the process for this review.

Intended purpose:
The 2012-2013 Federal Budget identified $55.7 million in savings from the Anti-Dementia Review[4], even before the review was completed. This would strongly suggest that price reductions were the pre-determined outcome from a postmarket review, rather than a focus on the evidence and quality use of medicines. The DUSC analysis on the utilisation and patterns of treatment of PBS listed drugs for type 2 diabetes (October 2012 and February 2013) and which forms the Terms of Reference 1 for this review, has already been used to recommend a price reduction for Fixed Dose Combination (FDC) glitpin/metformin products (April 2013 PBAC Meeting). As will be outlined below, measures of drug utilisation without aligned measures of outcomes do

[3] Colagiuri et al., DiabCost Australia 2003
[4] 2013-14 Budget, Budget Paper No. 2, Part 2 – Expense Measures, Post-market surveillance — review of Alzheimers Disease medications, Page 182 http://www.budget.gov.au/2013-14/content/bp2/html/bp2_expense-13.htm

not follow the Quality Use of Medicines principles and cannot be used to justify price reductions. There are additional unintended consequences of such actions –the resulting arbitrary price erosion (which is not based on any clinical evidence) of a comparator class, will mean that the opportunity to bring innovative diabetes therapies to the Australian diabetes community is severely limited and disadvantages people with diabetes in Australia.

Stakeholder Input and Terms of Reference (TOR):
There are multiple stakeholders in the field of diabetes, each with valuable and varied expertise which should be consulted as part of any review. In the development of the diabetes review, input into the process, the workflow, the timeframes and importantly the terms of reference should have been consultative with consumer, healthcare professional and industry input.

Unfortunately, the current TOR are limited in their potential to provide meaningful information and the timeframes associated with the process are entirely inadequate.

- *TOR 2: Consider if the utilisation of PBS listed drugs in current clinical practice represents expected cost effective use*
  - The utilisation of PBS listed drugs is available through the DUSC reports, however this provides only utilisation data and there is no information on outcomes, which is critical to inform any cost effectiveness decisions.
  - Determination of whether a treatment is cost effective in a chronic and complex disease like diabetes requires agreement on fundamental inputs such as, what is the appropriate long-term health economic model to use, what is an appropriate comparator, what are all of the health resource costs and inputs. The applicability, extrapolation, transformation and translation of clinical data through to an economic model are a significant component of a cost effectiveness submission to the PBAC, which usually takes 6-12 months to develop and has opportunity for multiple pre-submission meetings with the Department of Health and Aging to agree on relevant inputs.
- *TOR 3: Consolidate the clinical trial evidence used to support PBS listings of diabetes medicines listed since 2002 AND*
- *TOR 4: Collate and evaluate any additional clinical studies or meta-analyses for drugs currently PBS listed for T2DM that the Pharmaceutical Benefits Advisory Committee (PBAC) has not seen and that would inform their consideration.*
  - A systematic and comprehensive literature search and the associated analysis and interpretation of the findings to the level required for a PBAC submission on such a broad TOR as outlined above cannot be carried out in 6 weeks. Furthermore, other than studies directly provided by a sponsor to the PBAC as part of their own submissions in the past, it is unrealistic to expect a sponsor to know what the PBAC has or has not seen. These TOR would also seem to be more than a double-up of resources with each stakeholder presumably carrying out the same collation and presentation of data. It is also very difficult to know what information is required and what "…*that would inform their consideration"* actually means as the context of the review is not clear – is it just about cost effectiveness (as suggested in TOR 2) or about a

more holistic review of diabetes management in keeping with the principles of quality use of medicines.

If a stakeholder consultation had been an integral component of the review process then the issues highlighted above would have been identified and more appropriate and relevant TOR could have been developed, with appropriate time frames and work flows agreed upon in order to ultimately derive a truly meaningful review of diabetes in Australia.

Consistency and Transparency:
Novo Nordisk is concerned that there appears to be lack of consistency and clarity regarding the communication of scope for the review and a lack of transparency regarding the process.

Novo Nordisk is the leading supplier of insulin in Australia. In the letter to manufactures dated 3rd May 2013 (which Novo Nordisk did not receive), insulin products were clearly **not in scope** for this review. However, in notification received by Novo Nordisk on the 20th May, advising stakeholders of the call for public submissions to the review, the following statement was written:

> *We acknowledge that insulin is widely used in the management of T2DM although it is not the specific focus of this Review. However, the utilisation of insulin will provide context for medicines used in T2DM given the place of insulin in the clinical treatment algorithm for prescribers. Therefore, the information or data on the efficacy and safety of insulin compared to other medicines will be considered*

Without being the specific focus, it now appears that insulin will be considered, however, Novo Nordisk (and one presumes other insulin manufacturers) has had less time to respond to this review (and less clarity as to how insulin will be considered) than other sponsors. Although a difference of two weeks is not necessarily paramount, this is an example of an inconsistent process.

There is also a lack of transparency regarding the Expert Advisory Group which has been formed to provide advice on arising issues for the review. Although the Diabetes Review website states that the Advisory Group consists of experts in a range of fields relating to the management of diabetes such as endocrinologists, general practitioners, and diabetes educators, no additional information on the membership of this group is provided. As such, it is very difficult to ascertain the level of expertise relevant to the broader context of this review and it is also noticeable that the broader stakeholder groups are not represented (e.g. consumers, pharmacists, industry).

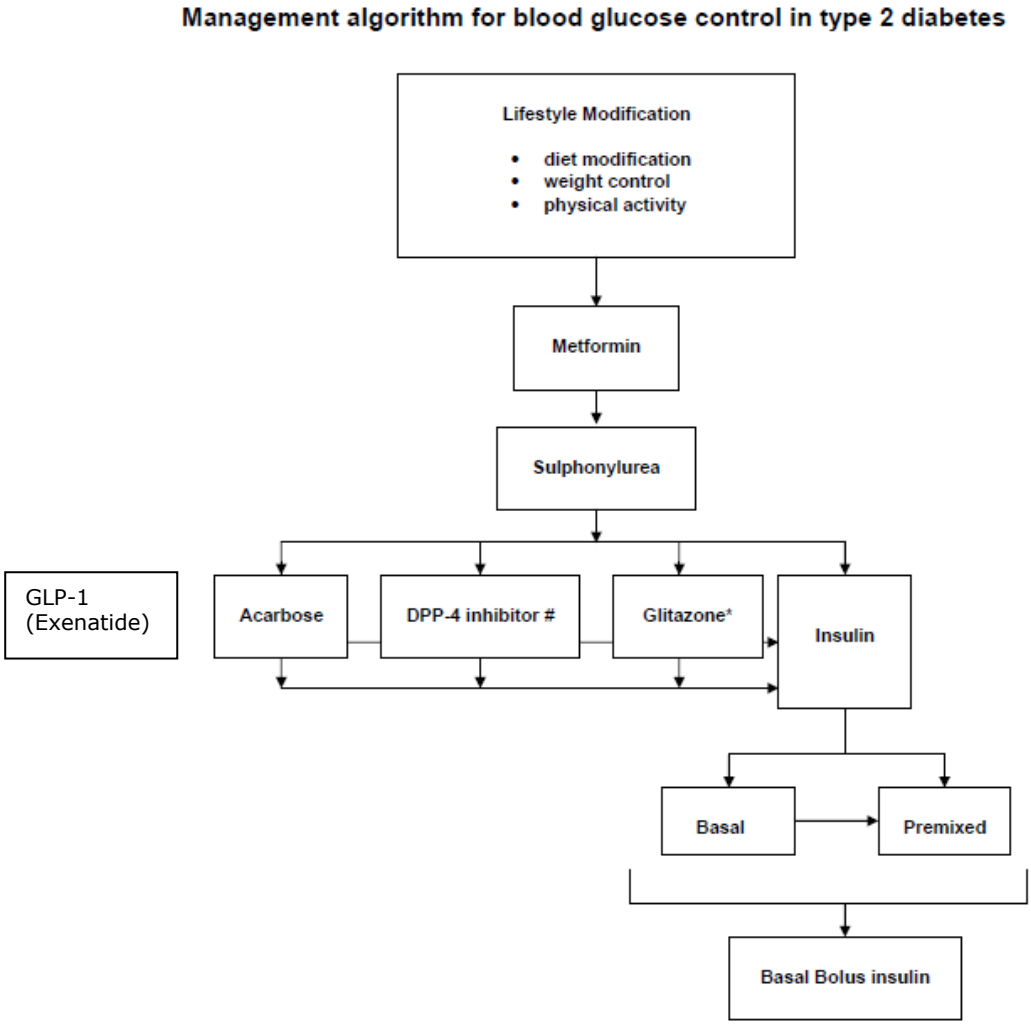
Notwithstanding what we believe to be significant concerns regarding the Diabetes Review, Novo Nordisk provides the following relevant information for due consideration.

3. Addressing the Specific Terms of Reference:

Type 2 diabetes is a chronic, heterogeneous and progressive disease which importantly, requires individualised and progressive treatment. The progressive loss of beta-cell function associated with type 2 diabetes, means that most patients will require insulin (which is still one of the most effective

hypoglycaemic agents) as part of their treatment regimen. Although insulin in general does not have any PBS restrictions, the NHMR National Evidence Based Guideline for Blood Glucose Control in Type 2 Diabetes (Colagiuri *et al.,* 2009) highlights the clinical positioning of insulin in Australia (Figure 2). Importantly, this algorithm only included therapies available through the PBS and at the time of publication, products in the GLP-1 class of therapies were not PBS listed. However, the February 2013 DUSC review (Item 7.4 pg 5), positions exenatide alongside the gliptins and glitazones (box added to Figure 2 to reflect this).

Figure 2:



Reproduced from the NHMRC National Evidence Based Guideline for Blood Glucose Control in Type 2 Diabetes (Colagiuri *et al.,* 2009)

Novo Nordisk notes the Department of Health and Aging (DoHA) Postmarket Review Website[5] statement which states that:

"We acknowledge that insulin is widely used in the management of T2DM although it is not the specific focus of this Review. However, the utilisation of insulin will provide context for medicines used in T2DM given the place of insulin in the clinical treatment algorithm for prescribers. Therefore, the information or

[5] http://www.pbs.gov.au/info/reviews/diabetes

data on the efficacy and safety of insulin compared to other medicines will be considered."

In order to address the terms of reference as effectively as possible, and in keeping with the statement of intent above, then Novo Nordisk has made the following assumptions:

1. The overwhelming majority of insulin usage in the Australian community (86.1%) is with insulin analogues[6] and therefore in order to provide relevant input to this review, systematic literature reviews have been designed to focus primarily on insulin analogues.
2. Clinical and real-world evidence comparing insulin with either acarbose, exenatide, gliptins or glitazones will be presented.
   - A comparison between different types of insulin or insulin regimens is not in scope for this review.
3. The insulin products in scope for Novo Nordisk in this Review are:
   - NovoMix® 30 (insulin aspart) – a premixed insulin analogue which is used to initiate insulin therapy in type 2 diabetes as well as intensify therapy as required.
   - NovoRapid® (insulin aspart) – a rapid acting insulin analogue which is used to supplement basal therapy in type 2 diabetes or as part of a more intensive basal/bolus therapy regimen.
   - Please note that Levemir® (insulin detemir) is not PBS listed for type 2 diabetes and is therefore not in scope for this review.

3.1. Term of Reference 1: Describe the utilisation and patterns of treatment of PBS listed drugs for T2DM, and compare these with PBS restrictions.

In October 2012 and February 2013, the DUSC reviewed reports on the utilisation and patterns of treatment of PBS listed drugs for type 2 diabetes which raised the following key issues which Novo Nordisk wishes to respond to.

1. The reports suggested that a proportion of prescriptions for some products did not meet the PBS criteria for prescribing. Although insulin does not have any PBS restrictions, Novo Nordisk has some general concerns regarding these reports.

    a. According to DoHA, the underlying purpose of Postmarket Reviews is to provide a more targeted and focused approach to National Medicines Policy objectives and Quality Use of Medicines (QUM) principles. The definition of QUM as defined in the DoHA National Strategy for Quality Use of Medicines Executive Summary[7] includes the following aspects:
        i. *Choosing suitable medicines if a medicine is considered necessary so that the best available option is selected by taking into account:*
            1. *the individual*

[6] IMS Retail Data 2013
[7] http://www.health.gov.au/internet/main/Publishing.nsf/Content/4CCAC8550BA36A52CA256F1800468A6E/$File/execsumbro.pdf

2. *the clinical condition– risks and benefits*
3. *dosage and length of treatment*
4. *any co-existing conditions*
5. *other therapies*
6. *monitoring considerations*
7. *costs for the individual, the community and the health system as a whole.*

ii. *Using medicines safely and effectively to get the best possible results by:*
1. *monitoring outcomes;*
2. *minimising misuse, over-use and under-use; and*
3. *improving people's ability to solve problems related to medication, such as negative effects or managing multiple medications.*

iii. *This definition of QUM applies equally to decisions about medication use by individuals and decisions that affect the health of the population.*

The DUSC reports focus solely on prescription data to ascertain adherence to PBS criteria. They do not however, in any way, capture the QUM clinical principles which clinicians consider each time they write a prescription:

- Who is the individual before them? What is their background and what are any relevant personal circumstances which might affect treatment options;
- What are the clinical considerations, co-morbidities and other medications for other disease states which must be taken into account?

All of these considerations lead to a justified clinical decision which cannot be captured by just looking at a prescription history.

Furthermore, the monitoring of outcomes is pivotal to any QUM assessment. However, the DUSC reports do not align the prescription data to any outcomes. They highlight that some products are being used outside the PBS criteria, but there is no way of knowing whether in fact the clinical outcomes justify this use. Conversely, a therapeutic product might be used entirely in accordance to PBS criteria, but not deliver any positive clinical outcomes in real life.

It is for this reason, that although the DUSC reports on utilisation provide interesting information which should be used to inform and guide dialogue with relevant stakeholders, they cannot be used to make any cost effectiveness or pricing recommendations.

2. The February 2013 report also included an analysis on insulin utilisation (Item 7.4b) and showed that nearly all prescriptions for insulin were for the PBS maximum quantity of 5 packs. This led DUSC to suggest that there was significant potential for wastage due to inadequate storage resulting in unusable insulin or due to a change of insulin type. Novo Nordisk disagrees with the DUSC suggestion that there is significant potential for wastage for the reasons outlined below.

    a. Type 2 diabetes is a chronic and progressive disease and treatment with insulin needs to be flexible. Unlike non-insulin diabetes

therapies which have fixed daily doses, a patient's daily insulin dose must be able to be modified or adjusted based on daily inputs (e.g food intake, exercise, lifestyle stresses etc.). Insulin doses are therefore by definition not fixed and consequently, monthly scripts are not appropriate. The current standard of a dispensed maximum quantity of 5x5x3ml (7500 units) and the time to refill basal, short/ultra-short and mixed insulin estimated by DUSC of 132, 120 and 99 days respectively, appear adequate and provide the flexibility, which people with diabetes and treated with insulin require. It is also important to note that monthly scripts would unnecessarily increase the cost to the patient.

b. The DUSC mean/median time for a patient to require re-supply for any of the insulin classes (basal, short, ultra-short, premix) are well below the 30mth shelf-life of most insulins. For example, the longest median time to re-supply reported was 132 days for a basal insulin pack (5x5x3ml, 7500IU) and this is well below the 30 month shelf-life. This also indicates that the average daily dose is approximately 57IU (7500IU/132d), which would lead to the estimate that one 3mL cartridge is used up in 5-6 days, which is before the in-use time of 1 month. Therefore, wastage of insulin in general is unlikely.

c. Novo Nordisk acknowledges the comment that insulin wastage could occur due to inadequate storage. However, based on an analysis of calls to our customer helpline centre we received less than 0.4% of calls in the last year (from a total of more than 7000 calls received), from patients or wholesalers (on behalf of patients) who stored their insulin outside of recommended temperature.

d. Furthermore, Novo Nordisk acknowledges the assumption that insulin may be wasted when people switch to other products and/or therapies. However, diabetes is a chronic and progressive disease where insulin is generally added (e.g. a patient on a basal-oral therapy may progress to basal-bolus therapy by adding a short acting insulin) or if a patient is switched from one regimen to another, then this is likely to only occur once or twice in the diabetes treatment cascade and therefore should not be seen as a recurring event and is not a major contributor to insulin wastage.

In summary, diabetes is a chronic and progressive disease which requires flexible and patient specific daily dosing and therefore monthly dispensing for insulin is not appropriate. Insulin is used within the required shelf-life and in-use time and is not wasted. Inadequate storage and insulin switching do not occur often and should not be seen as a major contributor to potential insulin wastage.

3.2 Term of Reference 2: Consider if the utilisation of PBS listed drugs in current clinical practice represents expected cost effective use;

and

Term of Reference 3: Consolidate the clinical trial evidence used to support PBS listings of diabetes medicines listed since 2002

As mentioned previously, in the timeframe provided for this Review, it is not feasible to carry out a comprehensive, systematic literature review and a thorough assessment of the resulting data to the standard which is required in a PBAC submission. Furthermore, a cost effective analysis for a chronic and complex disease state such as diabetes, requires extensive and complicated health economic modelling and access to critical data and information which again are not available as part of this Review or even possible in the timeframe.

Notwithstanding these significant limitations, Novo Nordisk has undertaken a systematic literature review and provides a top-line summary of the data.

Based on the DoHA definition of how insulin will be considered, Novo Nordisk undertook a systematic literature review from the year 2000 to present, comparing NovoRapid® and NovoMix® 30 with either Acarbose, glitazones, exenatide or gliptins. An overview of the search histories and results are presented in Table 2.

There are very few studies directly comparing insulin with oral or non-insulin injectable agents. The studies that have been identified all compared NovoMix® 30 either as a direct comparator or as an add-on therapy. The top-line results are outlined in Table 3 and in brief, NovoMix® 30 provides equivalent or significantly better improvements in HbA_{1c} than the comparators, and in many instances has a lower average daily cost. Using this most simplistic of analyses, then one can indeed say that in current clinical practice insulin is safe and efficacious and represents expected cost effective use.

Table 2: Search Strategies and Results from Systematic Literature Review comparing NovoRapid® and NovoMix® 30 with Gliptins, Exenatide, Acarbose or Glitazones

Database:MEDLINE, EMBASE, BIOSIS		Gliptins		Exenatide		Acarbose		Glitazones
Search Strategy		N		N		N		N
1	(aspart OR novomix OR novorapid) AND (type ADJ "2")	1880		1880		1880		1880
2	(DPP OR linagliptin OR sitagliptin OR saxagliptin OR vildagliptin OR gliptin)	14108	(GLP-1 OR exenatide OR byetta)	16083	(alpha ADJ glucosidase ADJ inhibitor)	4152	(rosiglitazone OR pioglitazone OR glitazone OR TZD)	36714
3	(Set-2 AND Set-1)	181		170		137		385
4	(Set-3) NOT (review) AND (English)[LA]	**53**		**61**		**42**		**133**
Exclusion Criteria								
A	Not the target population of type 2 diabetes	0		1		1		2
B	Does not report relevant outcomes	0		5				1
C	Does not contain sufficient subject numbers (n=25)	4		3		4		9
D	Not a randomised or observational study	40		20		21		61
E	Does not compare target product(s)	4		9		15		41
F	Duplicate	5		13		1		16
G	Data not available	0		7				
Excluded		**53**		**58**		**42**		**130**
Included		**0**		**3**		**0**		**3**

Table 3: Study Features and Results from Systematic Literature Review comparing NovoRapid® and NovoMix® 30 with Gliptins, Exenatide, Acarbose or Glitazones

Publication	Comparator Treatments	Trial Design	Patient Characteristics	Duration	HbA_{1c}	Hypoglycaemia	Weight	Adverse Events	Estimated Cost[a] to Commonwealth
NovoMix® 30 or NovoRapid® Vs Acarbose n=0									
NovoMix® 30 or NovoRapid® Vs Gliptins n=0									
NovoMix® 30 or NovoRapid® Vs Glitazones n=3									
Harrison *et al.,* Diabetes Care 2012; 35:1406-1412	NM30/MET (n=29) vs MET/PIO/SU (n=29)	Single centre, open label, RCT	Newly diagnosed type 2; 21-70 years age; HbA_{1c}>7%	3.5yrs	HbA_{1c} EOT: NM30/MET =6.4% MET/PIO/ SU = 6.6% No statistical difference p=0.54	No significant difference between groups (p=0.83)	Change Weight EOT: NM30/MET =4kg MET/PIO/ SU = 9.6kg No statistical difference p=0.35	No significant differences reported	NM30 dose EOT= 87U/day $3.07/day MET dose EOT = 2g/day $0.35/day Total NM30/MET cost/day = $3.42/day
									MET dose EOT = 2g/day $0.35/day SU (Glibenclamide) dose EOT =10mg/day $0.23/day PIO dose EOT= 45mg day $2.58/day Total MET/PIO/SU=$3.16 /day

Publication	Comparator Treatments	Trial Design	Patient Characteristics	Duration	HbA_{1c}	Hypoglycaemia	Weight	Adverse Events	Estimated Cost[a] to Commonwealth
Raskin *et al.,* Diabetes, Obesity and Metabolism 2009; 11:27-32	NM30/MET/ PIO (n=102) vs MET/PIO (n=98)	Multi centre, open label RCT	Insulin naïve type 2; ≥18 years of age; HbA_{1c} ≥7.5% and ≤12%	34 wk	HbA_{1c} EOT: NM30/MET/ PIO =6.5% (mean change from baseline -1.5%) MET/PIO = 7.8% (mean change from baseline -0.2%) Reduction in HbA_{1c} significantly better for NM30/MET/ PIO vs MET/PIO p<0.0001	Rate of minor hypoglycaemia greater in NM30/MET/PIO group than MET/PIO group p<0.05	Weight gain greater in NM30/MET/ PIO group Change Weight EOT: NM30/MET/ PIO = +4.6kg NM30 MET/PIO =+0.8kg P<0.0001	No significant differences reported	NM30 dose EOT[b] ~54U/day $1.90/day MET dose EOT ~2.4g/day $0.42/day PIO dose EOT = 30mg/day $2.04/day Total NM30/MET/PIO= $4.36/day MET dose EOT ~2.4g/day $0.42/day PIO dose EOT = 30mg/day $2.03/day Total MET/PIO= $2.45/day
Raz et al., Clinical Theraeutics 2005; 27:1432-1443	NM30 (n=97) vs NM30/PIO (n=93) vs SU/PIO (n=93)	Multi centre, multi-national open label RCT	Insulin naïve type 2 failing on SU treatment ≥18 years of age; HbA_{1c} between 7.4%- 14.7%	18 wk	Mean change from baseline: NM30 = -0.5% SU/PIO= -0.4% NM30/PIO = -1.2%	No major hypoglycaemia More minor hypoglycaemia reported in NM30 groups	Change Weight EOT: NM30= 2.2kg SU/PIO= 2.2KG NM30/PIO 4.0kg	More product related AE reported with NM30/PIO (28%) vs NM30 (20%) vs SU/PIO (16%)	NM30 dose EOT[b] ~60U/day $2.11/day SU/PIO SU dose EOT 14mg ~$0.32/day PIO dose EOT 30mg/day $2.03/day Total SU/PIO = $2.35/day

Publication	Comparator Treatments	Trial Design	Patient Characteristics	Duration	HbA_{1c}	Hypoglycaemia	Weight	Adverse Events	Estimated Cost[a] to Commonwealth
					NM30/PIO HbA_{1c} reduction significantly greater than NM30 mono (p=0.008) or SU/PIO (p=0.005)				NM30/PIO NM30 ~43U/day $1.52 PIO 30mg/day $2.03 Total NM30/PIO = $3.55/day
NovoMix 30 or NovoRapid Vs exenatide n=3									
Gallwitz et al., Diabetes Care 2011; 34: 604-606	Exenatide (BD)/MET (n=181) vs NM30/MET (BD) (n=173)	Multi centre, open label RCT	Metformin treated adults with type 2 diabetes and HbA_{1c} between 6.5% and 10%	26 wk	Mean change from baseline: Exenatide/ MET = -1.0% NM30/MET = -1.14% Not statistically different	No difference in major or nocturnal hypoglycaemai Percentage of patients with at least 1 minor hypoglycaemic episode was significantly greater with NM30/MET vs exenatide/MET	Change Weight EOT: Exenatide/ MET = -4.1kg NM30/MET = +1.0kg P<0.001	Significantly more withdrawals due to AEs with Exenatide/ MET (7.2%) vs NM30/MET (0.6%) p=0.0014 Main reason was nausea and diarrhea	Exenatide daily cost=$5.88 MET 2g/day $0.35/day Total Exenatide/MET = $6.23 NM30 EOT Dose = 28.4U/day $1.00/day MET 2g/day $0.35/day Total NM30/MET= $1.35/day
Bergenstal et al., Current Medical Research and Opinions 2009; 25:65-75	Exenatide/ MET/SU (n=124) vs NM30 (OD)/MET/SU (n=124) vs	Multi centre, open label RCT	Insulin naïve type 2 patients using MET/SU Aged between 18-80 years	24 wk	Mean HbA1c change from baseline: Exenatide/ MET/SU = -1.75%	Greater rates of minor hypoglycaemia reported in NM30 OD and BD compared with exenatide (4.02; 5.25	Change Weight EOT: Exenatide/ MET/SU = -1.9kg	More subjects withdrew from study with exenatide (30%) vs NM30 OD	Exenatide daily cost=$5.88 MET dose EOT[c] = 2g/day $0.35/day

Publication	Comparator Treatments	Trial Design	Patient Characteristics	Duration	HbA_{1c}	Hypoglycaemia	Weight	Adverse Events	Estimated Cost[a] to Commonwealth
	NM30 (BD) /MET (n=124)		$HbA_{1c} \geq 8.0\%$		NM30 (OD) /MET/SU = -2.34% NM30 (BD) /MET/SU = -2.76% NM30 OD and BD reduced HbA_{1c} significantly more than exenatide (p<0.0001)	and 1.28 events/subject year respectively) p<0.0001. Major hypoglycaemia reported by 4 subjects using NM30 OD, 6 subjects using NM30 BD and no subjects using exenatide.	NM30 (OD) /MET/SU = +2.8kg NM30 (BD) /MET/SU = 4.1kg	(16%) or NM30 BD (19%). The primary reason for discontinuation in the exenatide group was nausea. 29% of subjects experience nausea with exenatide vs 9% with NM30 OD and 8% with NM30 BD	SU (Glibenclamide) dose EOT[c] =10mg/day $0.23/day Total Exenatide/MET/SU = $6.46/day NM30 OD EOT Dose= 44.9U/day $1.58/day MET dose EOT[c] = 2g/day $0.35/day SU (Glibenclamide) dose EOT[c] =10mg/day $0.23/day Total NM30 OD/MET/SU = $2.16/day NM30 BD EOT dose = 96.1U/day $3.39/day MET dose EOT[c] = 2g/day $0.35/day Total NM30 BD/MET = $3.74/day

Publication	Comparator Treatments	Trial Design	Patient Characteristics	Duration	HbA_{1c}	Hypoglycaemia	Weight	Adverse Events	Estimated Cost[a] to Commonwealth
Nauck et al., Diabetologia 2007; 50: 259-267	Exenatide/ MET/SU (n=253) vs NM30 (BD)/MET/SU (n=248)	Multi centre, multi-national open label RCT	Insulin naïve type 2 failing on MET/SU treatment Aged between 30-75 years HbA_{1c} $\geq$7.0% and $\leq$11.0%	52 wk	Mean HbA_{1c} change from baseline: Exenatide/MET/SU = -1.04% NM30 (BD)/MET/SU = -0.89% No significant difference p=0.067	Overall, daytime and nocturnal hypoglycaemia rates were the same, no major hypoglycaemia reported	Change Weight EOT: Exenatide/ MET/SU = -2.5kg NM30 (BD) /MET/SU = +2.9kg P<0.001	More TEAEs occurred in the exenatide treated cohort (70.8%) vs the NM30 cohort (49.6%) and this was mainly driven by nausea.	[d]Exenatide daily cost=$5.88 [d]NM30 EOT dose = 24.4U/day $0.86/day

[a]Costs estimated using published cost of DPMQ http://www.pbs.gov.au/browse/body-system Accessed June 2013. Note that based on the Therapeutic Relativity Sheets special pricing arrangements apply to certain medications
[b]Weight of patients not reported in publication. Therefore average weight of patients was estimated from BMI reported in publication using average height of adults in USA reported in Anthropometric Reference Data for Children and Adults: United States, 2007–2010 http://www.cdc.gov/nchs/data/series/sr_11/sr11_252.pdf. This was then used to estimated average daily dose of insulin used.
[c]Final doses of MET/SU not reported in publication, therefore assumption based on standard doses applied consistently
[d]Doses of MET/SU not reported in publication but assumed to be the same for both treatment groups and therefore only cost of exenatide vs NM30 is shown
MET = Metformin; SU = sulphonylurea; PIO = pioglitazone; NM30 = NovoMix® 30; EOT = End Of Trial; OD = once daily; BD = twice daily

3.3 Term of Reference 4: Collate and evaluate any additional clinical studies or meta-analyses for drugs currently PBS listed for T2DM that the Pharmaceutical Benefits Advisory Committee (PBAC) has not seen and that would inform their consideration.

Notwithstanding the significant limitations to this TOR outlined previously, additional studies which may be interesting for the PBAC to consider are real-world or observational studies and database analyses. These studies/analyses usually are carried out in very large populations across wide geographic areas and assess the impact of a medication in real life without the strict and sometimes artificial environment of a randomised clinical trial.

Novo Nordisk undertook a systematic literature review from the year 2000 to present, reviewing the use of NovoRapid® and NovoMix® 30 outside of a clinical trial setting. An overview of the search histories and results are presented in Table 4.

Table 4: Search Strategies and Results from Systematic Literature Review of NovoRapid® and NovoMix® 30 in Real World or Observational Studies

Database:MEDLINE, EMBASE, BIOSIS		
Search Strategy		N
1	(aspart OR novomix OR novorapid) AND (type ADJ "2")	1880
2	(real ADJ world) OR (observational)	188959
3	(Set-2 AND Set-1)	189
4	(Set-3) NOT (review) AND (English)[LA]	**150**
Exclusion Criteria		
A	Not the target population of type 2 diabetes	4
B	Does not report relevant outcomes	12
C	Does not contain sufficient subject numbers (n=25)	2
D	Not a randomised or observational study	4
E	Does not compare target product(s)	25
F	Duplicate	56
G	Data not available	10
Excluded		**113**
Included		**37**

The studies can be broadly divided into 2 categories:

1. those which monitored the outcomes of initiating NovoMix® 30 or NovoRapid® following oral hypoglycaemic agent failure – this highlights the use of insulin as a progressive treatment
2. those which monitored the outcomes of switching patients from previous insulin use to either NovoMix® 30 or NovoRapid®.

Of the 37 documents identified:

- Six (6) documents report on country specific or subgroup analyses from the A_1chieve study. A_1chieve was the largest observational study ever conducted in insulin therapy (more than 65,000 people), and explored

both the progression of diabetes treatment with insulin initiation in insulin naïve patients, as well as the outcomes of switching patients from previous insulin use to an insulin analogue. A_1chieve was carried out in 28 different countries across four continents. For the purpose of this submission, the total cohort results as reported by Home *et al.,* 2011 are described in more detail.

- Fifteen (15) documents report on country specific or subgroup analyses from the IMPROVE™ study. The IMPROVE™ study was a multinational, non-randomised, non-interventional, observational study carried out in 11 countries across three continents, and specifically investigated the safety and efficacy of NovoMix® 30 in the treatment of over 50,000 patients with type 2 diabetes. For the purpose of this submission, the total cohort results as reported by Valensi *et al.,* 2009 are described in more detail.

- Eight (8) documents report on country specific or subgroup analyses from the Physicians' Routine Evaluation of Safety and Efficacy of NovoMix® 30 Therapy (PRESENT) study. PRESENT collected data on the safety and efficacy of using NovoMix® 30 either as monotherapy or in combination with oral agents in over 20,000 patients with type 2 diabetes in 13 countries. For the purpose of this submission, the total cohort results as reported by Khutsoane *et al.,* 2008 are described in more detail.

- Two (2) documents report on the UpGrade study which compared patients with type 2 diabetes taking either soluble human insulin or NovoRapid®. The full dataset and a subgroup analysis of elderly patients is presented.

- Six (6) additional studies report on individual observational and cohort studies and a brief summary of the data are presented.

A_1chieve:
The A_1chieve study was a 24 week, international, prospective, multicentre, non-interventional and observational study of people with type 2 diabetes using either Levemir®, NovoMix® 30 or NovoRapid®. The study was carried out in 28 countries across Asia, Africa, Latin America and Europe, grouped into seven geographical regions: China; South Asia (Bangladesh, India, Pakistan); East Asia (Indonesia, Korea, Malaysia, Philippines, Singapore, Taiwan); north Africa (Algeria, Morocco, Tunisia, Libya); Middle East/Gulf (Egypt, Iran, Jordan, Turkey, Bahrain, Kuwait, Oman, Qatar, Saudi Arabia, UAE, Yemen); Latin America (Argentina, Mexico) and Russia. Participants were recruited between January 2009 and June 2010. The insulin therapies were prescribed by a physician in the course of normal clinical practice and the safety and effectiveness of therapy were determined from measurements made at usual clinic visits.

Although patients were prescribed Levemir®, NovoMix® 30 or NovoRapid® as part of their therapy, the vast majority in both the insulin naïve and prior insulin user cohorts used NovoMix® 30 (Table 5).

Table 5: Number of patients using each insulin analogue

	Insulin naïve				Prior insulin users			
	NM30	Levemir®	NR alone	NR + basal	NM30	Levemir®	NR alone	NR + basal
N	27,591	12,078	2751	1593	13,318	3467	1145	2512

NM30 – NovoMix® 30; NR- NovoRapid®

A summary of the results of the combined insulin analogues is provided in Table 6. In brief, the total cohort achieved a significant improvement in HbA_{1c} of 2.1%, with significant reductions in the rates of hypoglycaemia and without weight gain. Those patients naïve to insulin improved their HbA_{1c} by 2.2%, did not experience significant increases in overall hypoglycaemia or weight gain, while patients who were previous insulin users, improved their HbA_{1c} by 1.8%, significantly decreased their rates of hypoglycaemia and without any additional weight gain.

IMPROVE ™:

The IMPROVE™ study was a 26 week observational study carried out in 11 countries: Canada, China, Greece, Gulf region, India, Iran, Italy, Japan, Poland, Russia and South Korea. The study aimed to investigate the safety and efficacy of NovoMix® 30 when prescribed in routine practice by clinicians in both primary and secondary care settings. The combined global results from Canada, China, Greece, India, Italy, Japan, Poland and Russia are outlined in Table 6. In brief, the total cohort achieved a significant improvement in HbA_{1c} of 2.3%, with significant reductions in the rates of hypoglycaemia and without weight gain. Those patients naïve to insulin improved their HbA_{1c} by 2.1%, had small increases in overall hypoglycaemia without any weight gain, while patients who were previous insulin users, improved their HbA_{1c} by 2.0%, significantly decreased their rates of hypoglycaemia and without any additional weight gain.

It is also very interesting to note that patient overall treatment satisfaction increased substantially from baseline to end-of-study, with a greater proportion of patients in all countries, extremely/very satisfied with their diabetes treatment after NovoMix® 30 therapy, compared with previous therapy (Table 7).

Table 7: Treatment satisfaction with NovoMix® 30.

	Proportion of Patients Extremely/Very Satisfied with Treatment (%)	
	Baseline	End-Of-Study
Total Cohort	10.0	59.2
Insulin Naïve	9.0	59.3
Prior Insulin User	13.3	58.5

PRESENT:

The Physicians' Routine Evaluation of Safety and Efficacy of NovoMix® 30 Therapy (PRESENT) study was a 6-month, prospective, uncontrolled, clinical experience evaluation study among clinicians who used NovoMix® 30 for patients with type 2 diabetes in daily clinical practice in 13 countries: India, Iraq, Jordan, Lebanon, Romania, Russia, Saudi Arabia and the Gulf countries (Kuwait, Qatar and the United Arab Emirates), South Africa, South Korea and Turkey. The clinical management using NovoMix® 30 (dosage and injection regimen) was entirely at the discretion of the clinician and according to routine clinical practice. The safety and efficacy of NovoMix® 30 used either as monotherapy or in combination with oral agents is outlined in Table 6. In brief, the total cohort

achieved a significant improvement in HbA_{1c} of 1.8%, with significant reductions in the rates of hypoglycaemia and without weight gain. Those patients naïve to insulin improved their HbA_{1c} by 2.1%, significantly decreased their rates of hypoglycaemia and without any additional weight gain. The prior insulin users (the majority of whom were on human insulin) were divided into those who had been on insulin only and those on insulin and oral agents. The patients on insulin only improved their HbA_{1c} by 1.45%, significantly decreased their rates of hypoglycaemia and without any weight gain. The patients on insulin and oral agents also improved their HbA_{1c} by 1.47%, significantly decreased their rates of hypoglycaemia and without any weight gain.

UpGrade:

The UpGrade study was a 26-week multicentre, open-label, non-randomised, non-interventional observational study to assess the safety and efficacy of soluble human insulin and NovoRapid® in patients with type 2 diabetes. Patients were recruited into the study if they were taking either soluble human insulin or NovoRapid® for between 3 months and 3 years. The primary endpoint in this study was a comparison of the number of major hypoglycaemic episodes. A summary of the results is presented in Table 8, but in brief, treatment with NovoRapid® was associated with a lower rate of hypoglycaemia and a greater reduction in HbA_{1c} compared with soluble human insulin. A sub-analysis looking at elderly patients (>70 years of age) (n=1385) also demonstrated a significantly lower risk of major and minor hypoglycaemia and a greater reduction in HbA_{1c} with NovoRapid® compared with soluble human insulin.

Table 8: Results from the UpGrade Study (Cucinotta *et al.,* 2012[8])

	Soluble Human Insulin	NovoRapid®
Number of patients	977	3103
Insulin regimen		
Bolus only	20%	12%
Basal Bolus	45%	63%
Bolus Mix	35%	25%
Hypoglycaemic event/patient year		
Major	0.122	0.115
Minor	9.530	6.648
HbA_{1c}	Baseline=7.82% EOT = 7.60% Mean change = -0.22% p<0.0001	Baseline=8.02% EOT = 7.63% Mean change = -0.39% p<0.0001

EOT = End of Trial

[8] Cucinotta *et al.,* Minerva Endocrinology 2012;37:357-366

Table 6: Study Features and Results from Systematic Literature Review of NovoRapid® and NovoMix® 30 in Real World or Observational Studies.

Publication		Duration	HbA_{1c}	Hypoglycaemia	Weight
A_1chieve: Home *et al.,* Diabetes Research Clinical Practice 2011; 94: 352-363					
Total Cohort	N=66,726	24 wks	Baseline=9.5% EOT = 7.4% Mean change = **-2.1%** p<0.001	Events/person year Overall : Baseline= 3.11 EOT=1.61 p<0.0001 Minor: Baseline= 2.79 EOT=1.60 p<0.0001 Nocturnal: Baseline= 0.93 EOT=0.36 p<0.0001 Major: Baseline= 0.33 EOT=0.01 p<0.0001	Baseline= 73.3kg EOT=73.3kg
Progression (insulin naïve)	N=44,872		Baseline=9.5% EOT = 7.4% Mean change = **-2.2%** p<0.001	Events/person year Overall : Baseline= 1.07 EOT=1.19 p=0.1713 Minor: Baseline= 0.98 EOT=1.18 p=0.0056 Nocturnal: Baseline= 0.28 EOT=0.26 p=0.0012 Major: Baseline= 0.09 EOT=0.00 p<0.0001	Baseline= 72.1kg EOT=72.2kg
Prior insulin use	N=21,854		Baseline=9.4% EOT = 7.6% Mean change = **-1.8%** p<0.001	Events/person year Overall : Baseline= 7.31 EOT=2.48 p<0.0001 Minor: Baseline= 6.50 EOT=2.47 p<0.0001 Nocturnal: Baseline= 2.24 EOT=0.58 p<0.0001 Major: Baseline= 0.81 EOT=0.01 p<0.0001	Baseline= 75.7kg EOT=75.7kg

Publication		Duration	HbA_{1c}	Hypoglycaemia	Weight
IMPROVE™: Valensi *et al.,* International Journal of Clinical Practice 2009; 63: 522-531					
Total Cohort[1]	N=52,419	26 wks	Baseline=9.3% EOT = 7.1% Mean change = **-2.3%** p<0.0001	Events/person year Minor: Baseline= 2.77 EOT=2.62 NS Nocturnal: Baseline= 0.78 EOT=0.55 NS Major: Baseline= 0.094 EOT=0.008 NS	Baseline= 70.5kg EOT=70.5kg
Progression (insulin naïve on oral agents only)	33,797		Baseline=9.2% EOT = 7.1% Mean change = **-2.1%** p<0.0001	Minor: Baseline= 2.11 EOT=2.48 p<0.001 Nocturnal: Baseline= 0.50 EOT=0.55 p<0.001 Major: Baseline= 0.071 EOT=0.006 p<0.001	Baseline= 70.6kg EOT=70.5kg
Prior insulin use	9,568		Baseline=9.3% EOT = 7.3% Mean change = **-2.0%** p<0.0001	Minor: Baseline= 8.11 EOT=3.23 p<0.001 Nocturnal: Baseline= 2.66 EOT=0.61 p<0.001 Major: Baseline= 0.269 EOT=0.021 p<0.001	Baseline= 71.5kg EOT=71.5kg
PRESENT: Khutsoane *et al.,* Diabetes Obesity and Metabolism 2008; 10: 212-222					
Total Cohort[2]	N=21,977	6 months	Baseline=9.52% EOT = 7.71% Mean change = **-1.81%** p<0.001	Events/person year Minor: Baseline= 5.0 EOT=2.1 p<0.001 Nocturnal: Baseline= 1.9 EOT=0.6 p<0.001 Major: Baseline= 0.36 EOT=0.09 p<0.001	Baseline=73.58kg EOT=73.26kg

Publication		Duration	HbA_{1c}	Hypoglycaemia	Weight
Progression (insulin naïve on oral agents only)	8583		Baseline=9.77% EOT = 7.62% Mean change = **-2.15%** p<0.001	Minor: Baseline= 2.2 EOT=2.0 p<0.001 Nocturnal: Baseline= 1.1 EOT=0.55 p<0.001 Major: Baseline= 0.18 EOT=0.09 p<0.001	Baseline=74.22kg EOT=74.03kg
Prior insulin only use	5942		Baseline=9.18% EOT = 7.73% Mean change = **-1.45%** p<0.001	Minor: Baseline= 8.7 EOT=2.1 p<0.001 Nocturnal: Baseline= 3.2 EOT=0.55 p<0.001 Major: Baseline= 0.7 EOT=0.05 p<0.001	Baseline=72.21kg EOT=71.89kg
Prior insulin and OAD use	4673		Baseline=9.25% EOT = 7.78% Mean change = **-1.47%** p<0.001	Minor: Baseline= 7 EOT=2.3 p<0.001 Nocturnal: Baseline= 2.74 EOT=0.68 p<0.001 Major: Baseline= 0.45 EOT=0.18 p<0.001	Baseline=74.67kg EOT=74.31kg

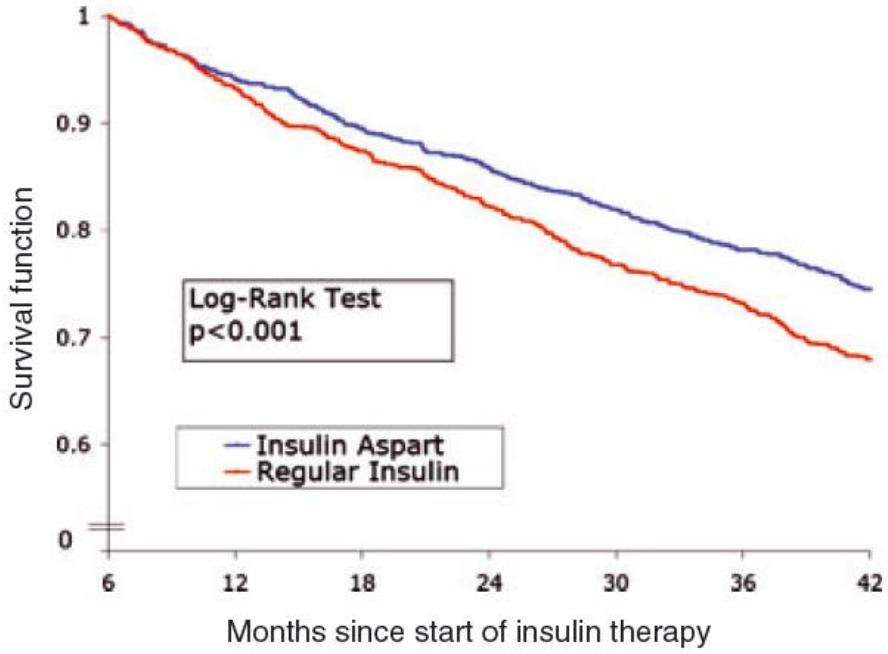
[1] 17% of the total cohort is comprised of patients who had not had any previous pharmaceutical therapy; [2] 8% of the total cohort is comprised of patients who had not had any previous pharmaceutical therapy

EOT = End of Trial

Additional studies were identified reporting on real world usage of insulin analogues and a summary of the results are provided in Table 9. In summary all of the studies have demonstrated a significant improvement in HbA_{1c}, without weight gain and without any safety issues.

A final study reviewed the incidence of recorded macro- and microvascular events in type 2 diabetes patients treated with either NovoRapid® or soluble human insulin in general practice throughout Germany (Rathmann and Kostev 2013[9]). The IMS HEALTH Disease Analyzer database was used to identify patients on either NovoRapid® or soluble human insulin and they were matched for age, sex, diabetes treatment period and type of health insurance and there were 3154 patients included in each group. The incident macro- and microvascular complications recorded in the database were then compared. The recorded HbA_{1c} was lower for the NovoRapid® cohort (7.9%) compared with the soluble human insulin cohort (8.3%). Of specific interest, the NovoRapid® cohort were at a significantly lower risk of macrovascular complications compared with the soluble human insulin group ($p<0.001$) (Figure 3).

Figure 3: Kaplan-Meier Curves for macrovascular complication free survival of type 2 patients in primary care using either NovoRapid® or soluble human insulin.



Reproduced from: Rathman and Kostev 2013

In summary, the extensive literature describing the use of either NovoMix® 30 or NovoRapid® in the real world setting, demonstrates the significant advantages of using these insulin analogues to improve glycaemic control, reduce the risk of hypoglycaemia and improve treatment satisfaction for patients with type 2 diabetes.

[9] Rathmann and Kostev Diabetes Obesity and Metabolism 2013; 15: 358-363

Table 9: Study Features and Results from Systematic Literature Review of NovoRapid® and NovoMix® 30 in Real World or Observational Studies.

Publication		Duration	HbA_{1c}	Hypoglycaemia	Weight
Mäkelä JK et al., Diabetes Research and Clinical Practice 2012; 95: 10-18					
Use of NM30 in insulin naïve patients in Finland	N=215	26 wks	Baseline=8.5% EOT = 7.1% Mean change = **-1.4%** p<0.0001	Events/person year Minor: Baseline= 0.66 EOT=6.45 p<0.0001 Nocturnal: Baseline= 0.07 EOT=1.25 p<0.05 Major: Baseline= 0.13 EOT=0.20 NS	Baseline=89.9kg EOT=90.9kg
Use of NM30 in patients with prior insulin use in Finland	N=342		Baseline=8.6% EOT = 7.5% Mean change = **-1.1%** p<0.0001	Events/person year Minor: Baseline= 5.11 EOT=8.58 p<0.05 Nocturnal: Baseline= 2.21 EOT=2.56 NS Major: Baseline= 0.17 EOT=0.13 NS	Baseline= 91.0kg EOT=92.3kg
Berntorp *et al.,* Primary Care Diabetes 2011; 5: 89-94					
Use of NM30 in insulin naïve patients in Sweden	1154	6 months	Baseline=8.8% EOT = 7.2% Mean change = **-1.6%** p<0.0001	Events/person year Any event Baseline= 0.5 EOT=4.1 Nocturnal: Baseline= 0.1 EOT=0.9	Baseline= 86.1kg EOT=87.6kg

Publication		Duration	HbA_{1c}	Hypoglycaemia	Weight
Nobels *et al.,* Current Medical Research and Opinion 2012; 28: 1-10					
Use of NM30 in patients switching from human premixed insulin in Belgium and Luxembourg	N=592	26 weeks	Baseline=7.9% EOT = 7.56% Mean change = **-0.34%** p<0.001	Number of patients reporting an episode Any episode: Baseline=30.7% EOT=29.2% p<0.001 Minor: Baseline= 24% EOT=23% p<0.001 Nocturnal: Baseline= 6.9% EOT=5.8% p<0.001	Baseline=85.5kg EOT=85.6kg
Schroner and Uliciansky Diabetes 2009; 58 (Suppl 1) A536-A537 (Abstract only)					
Use of NM30 in patients switching from human insulin in Slovakia	N=483	3 months	Baseline=9.18% EOT = 7.89% Mean change = **-1.29%** p<0.001	Symptomatic and nocturnal hypoglycaemia decreased from baseline	Baseline=85.7kg EOT=85.0kg
Suchankova *et al.,* Value in Health 12 A405-A406 (Abstract only)					
Use of NM30 in patients switching from human premixed insulin in the Czech setting	N=831	24 week	Baseline=8.98% EOT = 7.91% Mean change = **-1.07%**	Reduction in major hypoglycaemia of 97% Reduction in minor hypoglycaemia of 80%	Not reported

NM30 = NovoMix® 30; EOT = End of Trial

4. Conclusion:

Type 2 diabetes is a chronic and progressive disease which is predicted to become the leading burden of disease in Australia in the next 5 years.

A review of diabetes management should therefore follow a holistic approach recognising that equal consideration must be given not only to clinical outcomes but also to important patient benefits such as reduced side effects, patient convenience and quality of life.

Only 7% of all direct healthcare costs for people with type 2 diabetes are comprised of diabetes medications, with the majority of costs associated with the management of diabetes complications. The presence of long term complications more than doubles the cost burden of diabetes management. As such, patients should have access to the latest advances in diabetes therapy and technologies, so that in the long term, diabetes complications and the associated costs can be reduced.

The current review of drug utilisation provides valuable information but without reviewing associated clinical and patient outcomes, then it does not follow the Quality Use of Medicines principles and cannot be used to argue cost effectiveness or justify price reductions.

As type 2 diabetes is a progressive disease, then insulin is the ultimate hypoglycaemic agent and a review of the current literature provides evidence to demonstrate that insulin is a safe, efficacious and low cost medication for the treatment of diabetes. A review of observational studies which have included over 100,000 subjects, further confirms the efficacy and safety of insulin analogues, which demonstrate significant improvements in HbA_{1c} and improvements in treatment satisfaction in real world settings.