

**APPLICATION FOR RECLASSIFICATION FOR  
PARACETAMOL & PHENYLEPHRINE  
COMBINATION**

**Paracetamol in combination with Phenylephrine**

**AFT Pharmaceuticals Ltd**

**to**

**Medicines Classification Committee (MCC)**

**For the 52<sup>nd</sup> Meeting**



## EXECUTIVE SUMMARY

This application seeks reclassification of paracetamol 500 mg in combination with more than 2.5 mg phenylephrine per tablet, capsule or caplet AND individually wrapped powders or sachets of granules containing 1000 mg of paracetamol in combination with more than 5 mg phenylephrine in each such powder or sachet from General Sale (20 tablets, capsules or caplets per pack or less/ 10 sachets per pack or less)/ Pharmacy Only (more than 20 tablets or capsules or caplets per pack/ more than 10 sachets per pack) to Pharmacist Only.

It has recently been found that administration of phenylephrine hydrochloride 10 mg in combination with 1000 mg paracetamol (two tablets) effectively doubles the bioavailability of phenylephrine and quadruples the maximum plasma concentration. This effectively gives a dose equivalent as if an individual had taken 20 mg phenylephrine hydrochloride, which could potentially increase the risk of cardiovascular side effects in susceptible individuals, such as those who are overweight/obese and/or elderly and also have undiagnosed or asymptomatic cardiovascular disease(s) that may be exacerbated by an increase of blood pressure.

Paracetamol and phenylephrine combinations have been available in NZ and the rest of the world since 2006 when phenylephrine was substituted for pseudoephedrine in cough and cold medications to restrict the availability of the methamphetamine precursor, pseudoephedrine. When this was done, it was a worldwide accepted standard to base this on the pharmacological similarity between the two decongestant compounds, despite no thorough safety or efficacy data being generated for the new combination of phenylephrine with paracetamol following the dosing recommended by the FDA monograph for OTC Nasal Decongestant Products (10 mg of phenylephrine every 4 hours to a maximum of 60 mg in 24 hours).

So the key element here is that the effective dose of phenylephrine is altered by the combination such that the original assumption does not apply since without alteration of the phenylephrine dose, the phenylephrine exposure is double that of the FDA monograph. However alteration of the phenylephrine dose when used in combination with paracetamol can restore the exposure of phenylephrine in line with the original OTC monograph, giving an effective dose of 10 mg phenylephrine.

**PART A**

**1. INTERNATIONAL NON-PROPRIETARY NAME (OR BRITISH APPROVED NAME OR US ADOPTED NAME) OF THE MEDICINE**

Paracetamol (INN, AAN, BAN)  
Acetaminophen (USAN, JAN)

Phenylephrine hydrochloride (INN, USAN, JAN)

**2. PROPRIETARY NAME(S)**

Maxiclear Sinus and Pain Relief  
(Paracetamol 500 mg, phenylephrine hydrochloride 5 mg)

Maxiclear Cold and Flu Relief  
(Paracetamol 500 mg, phenylephrine hydrochloride 5 mg)

[REDACTED]

[REDACTED]

**3. NAME OF THE COMPANY/ORGANISATION/INDIVIDUAL REQUESTION  
A CLASSIFICATION**

AFT Pharmaceuticals Ltd  
Level 1  
129 Hurstmere Road  
Takapuna  
Auckland  
NEW ZEALAND

**4. DOSE FORM(S) AND STRENGTH(S) FOR WHICH A CHANGE IS SOUGHT**

In tablets, capsules and caplets in which paracetamol 500 mg is combined with more than 2.5 mg phenylephrine per tablet, capsule or caplet.

In individually wrapped powders or sachets of granules in which paracetamol 1000 mg is combined with more than 5 mg phenylephrine per powder or sachet.

## 5. PACK SIZE AND OTHER QUALIFICATIONS

In packs containing any number of tablets, capsules or caplets containing paracetamol 500 mg in combination with more than 2.5 mg phenylephrine per tablet – Pharmacist only

In packs containing more than 20 tablets, capsules or caplets containing paracetamol 500 mg in combination with 2.5 mg phenylephrine or less per tablet, capsule or caplet – Pharmacy Only

In packs containing 20 or less tablets, capsules or caplets containing paracetamol 500 mg in combination with 2.5 mg phenylephrine or less per tablet, capsule or caplet – General Sale.

In packs containing any number of sachets of powder containing 1000 mg paracetamol in combination with more than 5 mg phenylephrine per sachet – Pharmacist Only.

In packs containing more than 10 sachets of powder containing 1000 mg paracetamol in combination with 5 mg phenylephrine or less per sachet – Pharmacy Only.

In packs containing 10 or fewer sachets of powder containing 1000 mg paracetamol in combination with 5 mg phenylephrine or less per sachet – General Sale

## 6. INDICATIONS FOR WHICH CHANGE IS SOUGHT

### *Sinus and Pain Relief*

For the temporary relief of sinusitis symptoms including sinus headache, sinus pain and nasal congestion. Reduces fever.

### *Cold and Flu Relief*

For the temporary relief of pain and discomfort associated with cold & flu symptoms such as headache, sore throat, painful sinuses.

## 7. PRESENT CLASSIFICATION OF THE MEDICINE

Packs containing 20 or less tablets, capsules or caplets containing paracetamol 500 mg in combination with phenylephrine per tablet (up to 250 mg phenylephrine per pack and 50 mg or less per recommended daily dose) is currently scheduled as General Sale.

Packs containing more than 20 tablets, capsules or caplets containing paracetamol 500 mg in combination with phenylephrine per tablet (up to 250 mg phenylephrine per pack and 50 mg or less per recommended daily dose) is currently scheduled as Pharmacy Only.

Packs containing more than 10 sachets of powder containing 1000 mg paracetamol in combination with phenylephrine per sachet (up to 250 mg phenylephrine per pack and 50 mg or less per recommended daily dose) is currently scheduled as Pharmacy Only.

Packs containing 10 or fewer sachets of powder containing 1000 mg paracetamol in combination with phenylephrine per sachet (up to 250 mg phenylephrine per pack and 50 mg or less per recommended daily dose) is currently scheduled as General Sale.

## 8. CLASSIFICATION SOUGHT

In packs containing any number of tablets, capsules or caplets containing paracetamol 500 mg in combination with more than 2.5 mg phenylephrine per tablet – Pharmacist Only

In packs containing more than 20 tablets, capsules or caplets containing paracetamol 500 mg in combination with 2.5 mg phenylephrine or less per tablet, capsule or caplet – Pharmacy Only

In packs containing 20 or less tablets, capsules or caplets containing paracetamol 500 mg in combination 2.5 mg phenylephrine or less per tablet, capsule or caplet – General Sale.

In packs containing any number of sachets of powder containing 1000 mg paracetamol in combination with more than 5 mg phenylephrine per sachet – Pharmacist Only.

In packs containing more than 10 sachets of powder containing 1000 mg paracetamol in combination with 5 mg phenylephrine or less per sachet – Pharmacy Only.

In packs containing 10 or fewer sachets of powder containing 1000 mg paracetamol in combination with 5 mg phenylephrine or less per sachet – General Sale

## 9. CLASSIFICATION STATUS IN OTHER COUNTRIES (ESPECIALLY AUSTRALIA, UK, USA AND CANADA) (Paracetamol 500 mg/phenylephrine 5 mg per tablet, capsule or caplet and paracetamol 1000 mg/phenylephrine 10 mg per sachet of powder/granules).

Australia	Not Scheduled/S1
United Kingdom	GSL (10 tablets), Pharmacy (20 tablets)
United States of America	Not Available (Limited to 325 mg paracetamol per tablet/capsule)
Canada	Not Available

**10. EXTENT OF USAGE IN NEW ZEALAND AND ELSEWHERE (EG SALES VOLUMES)**

**Table 1. IMS data extent of use of paracetamol and phenylephrine combinations in Australia, New Zealand and Asia.**

Country	Company	Product	Unit Sales 2012 - 2013	Sales USD 2012 - 2013
Australia	GlaxoSmithKline	Panadol Cold & Flu 20s	11	116
		Romilar CF CAP VARI 24s	17,821	163,309
	Johnson & Johnson	Sudafed PE VARI 24s	141,880	1,688,849
		Sudafed PE VARI 24s	38,338	739,294
		Sudafed PE 36s	0	0
		Sudafed PE 48s	0	0
		Sudafed PE FC Tab 500 mg + 5 mg 24s	80,451	758,852
		Sudafed PE FC Tab 500 mg + 5 mg 48s	18,583	294,865
		Sudafed PE Trip AC FC Tab 500 mg + 5 mg 20s	7,044	89,353
		Sudafed PE Trip AC FC Tab 500 mg + 5 mg 10s	7,455	60,854
		Codral PE COMBI 24s	1,225,204	12,338,489
		Codral PE COMBI 48s	672,863	10,869,019
		Codral 4 Flu COMBI 24s	44,655	476,791
		Codral 4 Flu COMBI 48s	31,520	504,597
		Codral PE CAP VARI 48s	198,324	3,194,046
		Codral PE CAP VARI 24s	238,310	2,413,658
		Aspen Pharma PL	CO PE Cold & Flu VARI 24s	201,448
	CO PE Cold & Flu VARI 48s		23,801	263,999
	Flutex FC Tab 500 mg + 5 mg 24s		8,362	41,866
	Pharmacare	PF Cold & Flu PE VARI 48s	234,016	2,650,343
		PF Cold & Flu PE VARI 24s	321,780	1,223,489
		PF Cold & Flu PE COMBI 24s	80,792	255,057
		PF Sinus/P/All PE COMBI 24s	0	0
		Trust Sin/Pain PE FC Tab 500 mg + 5 mg 24s	0	0
	Symbion	PC Cold & Flu VARI 24s	127,239	646,225
		PC Cold & Flu VARI 48s	49,743	420,380
	Alphapharm	TW Sinus Relief PE VARI 24s	5,478	50,852
	Amcal	CO PE Cold & Flu VARI 24s	128,438	656,673
		CO PE Cold & Flu COMBI 24s	16,857	89,877
	Generic Health P/L	P/A Cold & Flu Relief PE VARI 24s	39,954	717,865
	MSD	Demazin PE Cold & Flu VARI 24s	100,051	837,950
		Demazin PE Cold & Flu VARI 48s	44,518	592,668
		Demazin PE Cold & Flu COMBI 24s	35,867	300,080
Demazin PE Cold & Flu COMBI		20,793	279,602	

		48s		
	Chem-Mart	CM Cold & Flu VARI 48s	36,198	306,208
		CM Cold & Flu VARI 24s	58,450	297,485
		CM Cold & Flu COMBI 24s	11,208	58,739
		CM Cold & Flu FC Tab COMBI 24s	5,671	26,666
	Guardian	GRD PE Cold & Flu VARI 24s	37148	190,169
		GRD PE Cold & Flu COMBI 24s	0	0
	Orion	Cold & Flu PE PERR VARI 24s	56,162	162,804
		Cold & Flu PE PERR COMBI 48s	17,759	91,257
		Cold & Flu PE PERR VARI 48s	2,449	13,191
	Pharmacy Life	YP D/N Cold/Flu PE VARI 24s	24,672	129,812
		YP D/N Cold/Flu PE VARI 48s	12,132	48,714
		YP PE Sinus 24s	0	0
	AFT Pharmaceuticals	Maxiclear Tab 500 mg + 5 mg 24s	13,619	78,175
		Maxiclear Tab 500 mg + 5 mg 30s	0	0
	Pfizer	Robitussin CCF NT VARI 24s	5,585	63,977
		Robitussin CCF NT Tab 500 mg + 5 mg 30s	2,444	24,560
		Dimetapp CAP COMBI 48s	81,592	1,258,595
		Robitussin CCF NT CAP VARI 48s	48,152	733,270
		Robitussin CCF NT CAP VARI 24s	63,928	693,836
	Reckitt Benckiser	Lemsip CAP COMBI 16s	19,984	200,858
		Lemsip CAP 500 mg + 6.1 mg 12s	19,512	156,269
		Lemsip CAP 500 mg + 6.1 mg 16s	0	0
	Orion	MH Sinus Pain PE CAP 500 mg + 6.1 mg 24s	3,769	10,598
	Terry White Chem	TW Sinus Relief PE FC Tab 500 mg + 5 mg 24s	3,696	18,896
Indonesia	Konimex	Zeroflu tab COMBI 24s	1,051	98
	Kalbe Farma	Mextril Tab COMBI 100s	581,073	1,382,783
	Mega Farma	Fludane Plus Tab COMBI 100s	362,635	2,219,772
	First Medipharma	Emflu Tab COMBI 100s	0	0
	Itrasal Pharma	Paraflu Tab COMBI 100s	104,665	401,341
	Solas	Lodecon Tab COMBI 100s	13,107	30,285
	Transfarma Medika	Nipe CAP COMBI 100s	382	1,503
Philippines	Myra Pharm	Neozep Tab 500 mg + 10 mg 100	167,076	1,508,068
	Westmont	Decolgen Tab 500 mg + 10 mg 100	103,471	1,025,923
		Decolgen Tab 500 mg + 10 mg 4s	226,251	89,709
Vietnam	GSK (GlaxoSmithKline)	Panadol Cold & Flu Tab COMBI 96s	56,324	301,181
		Panadol Cold & Flu Tab COMBI 180s	22,274	147,997
	DHG Pharma	Hapacol CS Day Tab 650 mg + 5 mg 100s	65,467	183,154
	XL	Mefegesic Tab COMBI 100s	14,907	34,583
	NIC Pharma	Devaligen Extra Tab COMBI 100s	442	468
	Phapharco	Tuspi Daytime Tab COMBI 100s	1,566	3,549

	OPV	Ameflu Daytime New FC Tab COMBI 100s	91,007	340,466	
		Ameflu Day-C New FC Tab COMBI 100s	36,551	147,048	
		Ameflu Night New FC Tab COMBI 100s	14,583	54,892	
	Glomed-Toan Cau	Glotaldol F FC Tab COMBI 100s	62,132	269,473	
		Glotaldol Day FC Tab COMBI 120s	0	0	
	Stada	Flucoldstad FC Tab COMBI 100s	320	964	
	Thanh Nam Pharm	Merhu Flu FC Tab COMBI 100s	374	734	
Global Pharma	Coffnil FC Tab COMBI 100s	5,086	19,123		
Taiwan	GlaxoSmithKline	Panadol Cold & Flu Tab COMBI 160s	11,513	916,861	
		Panadol Cold & Flu Tab COMBI 400s	6,759	915,802	
		Panadol Cold & Flu Tab COMBI 192s	10,568	876,302	
		Panadol Cold & Flu Tab COMBI 320s	1,018	165,062	
	C.C.P.C.	Cold Tab COMBI 1000s	18	236	
	Genuine	Rhin Tab COMBI 144s	59	923	
	Hwangs Pharm	Take Common CAP COMBI 300s	40	1,543	
		Take Common CAP COMBI 240s	40	1,543	
		Take Common CAP COMBI 400s	0	0	
	Pfizer	Robitussin D&N, C&F FC tab VARI 12s	134,628	490,026	
Thailand	H.K. Pharmaceutical	COS 464 Tab COMBI 500s	24	259	
	Chankit Trading	Jetse Tab COMBI 500s	660	4,322	
New Zealand	Johnson & Johnson	Codral PE Tab VARI 24s	104,854	848,968	
		Codral PE Tab VARI 48s	18,401	280,463	
		Sudafed PE Tab VARI 24s	60,142	409,803	
		Sudafed PE Tab 500 mg + 5 mg 12s	0	0	
		Sudafed Tab Tab 500 mg + 5 mg 36s	0	0	
		Codral Tab COMBI 24s	6,772	58,100	
		Codral Tab COMBI 48s	0	0	
		Codral PE CAP COMBI 24s	47,660	367,766	
		Codral PE CAP COMBI 48s	15,501	179,485	
	GlaxoSmithKline	Panadol Tab VARI 24s	747	5,974	
		Panadol FC Tab 500 mg + 5 mg 20s	665	5,301	
		Panadol FC Tab VARI 48s	6,222	10,706	
		Panadol FC Tab COMBI 20s	888	7,154	
	AFT Pharmaceuticals	Maxiclear Tab 500 mg + 5 mg 30s	10,879	75,785	
		Maxiclear Tab 500 mg + 5 mg 60s	1,077	13,183	
		Maxiclear Tab 500 mg + 5 mg 10s	410	1,151	
		Maxiclear Tab 500 mg + 5 mg 1s	0	0	
	Orion		Cold & Flu PE PERR Tab VARI 24s	13,280	61,935



		Cold & Flu PE PERR Tab VARI 48s	5,631	32,947	
		Y/P SIN/PN REL PE CAP 500 mg + 6.1 mg 48s	3,224	18,925	
		Y/P SIN/PN REL PE CAP 500 mg + 6.1 mg 24s	4,561	16,692	
	Reckitt Benckiser	Lemsip Tab VARI 24s	4,175	41,888	
		Lemsip CAP 500 mg + 6.1 mg 16s	843	5,428	
	Pfizer	Dimetapp FC Tab VARI 24s	15,106	151,825	
		Dimetapp FC Tab VARI 48s	5,769	88,655	
Malaysia	Ranbaxy	Cheri 4 Flu FC COMBI 100s	7,502	23,210	
Hong Kong	GlaxoSmithKline	Panadol Cold & Flu Tab COMBI 30s	117,866	657,970	
		Panadol Cold & Flu Tab COMBI 20s	79,481	349,217	
		Panadol Cold & Flu COMBI 10s	19,934	46,106	
		Panadol Cold & Cough Tab COMBI 24s	27,693	129,803	
		Coldrex C Tab COMBI 20s	4,441	20,813	
		Coldrex Tab COMBI 20s	177	831	
	Advance Pharma	Neosed Tab COMBI 360s	12,172	616,019	
		Neosed Tab COMBI 15 x 12	1,932	65,830	
		Neosed Tab COMBI 15	984	2,230	
		Duoflue Cold Tab COMBI 1000	4,573	85,545	
		Duoflue Cold Tab COMBI 180	1,467	35,644	
	Fortune Pharmacal	Cotalin Tab COMBI 24s	32,726	195,932	
		Cotalin Tab COMBI 360s	1,026	87,171	
		Cotalin Tab COMBI 12s	481	3,829	
		Cotalin GP Extra Tab COMBI 288s	1,685	141,424	
		Cotalin GP Extra Tab COMBI 24s	3,938	25,260	
		Cotalin GP Extra Tab COMBI 96s	200	5,923	
		Cotalin GP Extra Tab COMBI 8s	2,389	5,703	
		Cotalin-ND Tab COMBI 288s	774	51,015	
		Cotalin-ND Tab COMBI 24s	3,627	22,123	
		Cotalin-ND Tab COMBI 12s	1,467	5,234	
		Cotalin-ND Tab COMBI 144s	121	4,282	
		Childrens Cotalin Tab COMBI 24s	615	3,979	
		Cotalin GP Tab COMBI 288s	276	17,006	
		Cotalin GP Tab COMBI 24s	1,191	6,989	
		Cotalin GP Tab COMBI 96s	60	1,622	
		Cotalin GP Tab COMBI 8s	235	589	
	Europharm	Flu-Zep Tab COMBI 1000s	4,754	102,265	
		Nildizz Cold Tab COMBI 10s	1,968	2,751	
		Maxicold Tab COMBI 12s	1,884	2,063	
		VIMIX COLD CAP COMBI 12s	81,221	84,604	
		FLU-OFF CAP COMBI 1000s	1,342	34,864	
		Coldsedin CAP COMBI 1000s	246	6,432	
			Coldsedin CAP COMBI 10s	1,968	2,564

		Grippidin CAP COMBI 10s	1,893	2,645
	Meyer Pharm	Kin-Cold Tab COMBI 10s	0	0
		Kin-Cold Tab COMBI 20s	0	0
		Menta CAP COMBI 1000s	4,688	23,111
		Menta CAP COMBI 12s	365	15,705
		Meracet CAP COMBI 1000s	406	17,141
		Meracet CAP COMBI 12	1,435	2,563
		Kin-Cold CAP COMBI 1000s		
	Marching Pharma	Flu-Zep COMBI 12s	0	0
	Loyal Advance	Neocod Tab COMBI 10s	0	0
	Unicorn	Kabol CAP COMBI 12s	50,023	88,795
	Vickman Lab	Decoldan CAP COMBI 10s	16,441	28,844
		Healtheon CAP COMBI 10s	13,326	19,277
		Onward CAP COMBI 10s	2,603	4,222
	Synco	Antiflu-N CAP COMBI 500s	1,691	33,519
	Neochem Pharm	Neosocol CAP COMBI 1000s	304	6,854
	Karen Pharm Co.	Carlyso CAP COMBI 10s	11,824	19,010
		Bromitane CAP COMBI 60s	0	0
		KarenCosed CAP COMBI 12s	0	0
	Nice Laboratory	Junicidin CAP COMBI 1000s	279	6,300
	Halsey Drug	Nasucap Decongest CAP COMBI 90s	267	2,870
	Merika Medicine	Merika Cold Relief CAP COMBI 10s	4,861	5,056
		Coldez Day + Night CAP COMBI 12s	0	0
	Vida Lab	Coldozet CAP COMBI 1000s	113	2,410
		Vidatapp Forte IMP CAP COMBI 1000	40	1,141
	Quality Pharma	Quali-Cold CAP COMBI 1000s	273	4,736
	Jean-Marie	Fluza CAP COMBI 500s	357	3,898
	APT Pharma	DF Multi-Symptom CAP COMBI 1000s	0	0
Singapore	GlaxoSmithKline	Panadol Cold & Flu Tab COMBI 20s	0	0
		Panadol C&F HR Kid Tab 500 mg + 5 mg 12s	40,876	148,479
	Sunward	Sunflu Tab COMBI 1000s	415	12,169
		SP-Febrax Tab COMBI 1000s	121	2,439
	Westmont	Decolgen No Drowse Tab 500 mg + 5 mg 20s	26,616	55,842
		Decolgen C&F + Vit C Tab COMBI 20s	9,347	21,511

#### 11. LABELLING OR DRAFT LABELLING FOR THE PROPOSED NEW PRESENTATIONS

Please see file marked “proposed artwork” on the CD and the corresponding tab in the hard copy.

## **12. PROPOSED WARNING STATEMENTS IF APPLICABLE**

Adults: Keep to the recommended dose. Do not take this medicine for longer than a few days at a time unless advised to by a doctor.

Children and adolescents: Keep to the recommended dose. Do not give this medicine for longer than 48 hours at a time unless advised to by a doctor.

Prolonged or excessive use can be harmful. If an overdose is taken or suspected, ring the Poisons Information Centre (Australia 13 11 26, New Zealand 0800 764 766) or go to hospital straight away even if you feel well because of the risk of delayed, serious liver damage.

Do not take with other cough or cold medicines or products containing paracetamol, unless advised to do so by a doctor or pharmacist  
Phenylephrine may cause sleeplessness in some people.

See your doctor before taking this product if you have high blood pressure, heart problems, if you are breastfeeding or taking anti-depressant medication.

## **13. OTHER PRODUCTS CONTAINING THE SAME ACTIVE INGREDIENT(S) AND WHICH WOULD BE AFFECTED BY THE PROPOSED CHANGE**

Codral Relief Cold & Flu + Decongestant (16 capsules)  
[Johnson & Johnson (NZ) Limited]

Cold & Flu Relief + Decongestant (20 tablets)  
[Multichem NZ Limited]

Coldrex PE Phenylephrine Congestion Clear (20 tablets)  
[GlaxoSmithKline (NZ) Ltd]

Coldrex PE Phenylephrine Sinus (20 tablets)  
[GlaxoSmithKline (NZ) Ltd]

Lemsip flexi Cold & Flu caplets Blackcurrant (6, 12 and 18 tablets)  
[Reckitt Benckiser (NZ) Ltd]

Lemsip flexi Cold & Flu caplets Lemon & Passionfruit (6, 12 and 18 tablets)  
[Reckitt Benckiser (NZ) Ltd]

Lemsip Max Cold & Flu with Decongestant Capsules (16 capsules)  
[Reckitt Benckiser (NZ) Ltd]

Lemsip Sinus + Pain Relief Capsules (16 capsules)  
[Reckitt Benckiser (NZ) Ltd]

Panadol Cold & Flu Max + Decongestant (20 tablets)  
[GlaxoSmithKline (NZ) Ltd]

Panadol Sinus Pain & Congestion Relief (20 tablets)  
[GlaxoSmithKline (NZ) Ltd]

Panadol Sinus Relief PE (20 tablets)  
[GlaxoSmithKline (NZ) Ltd]

Sinutab PE Phenylephrine Sinus & Pain Relief (12 tablets)  
[Johnson & Johnson (NZ) Ltd]

Sudafed PE Phenylephrine Sinus & Pain Relief (10 or 20 tablets)  
[Johnson & Johnson (NZ) Ltd]

## **PART B**

### **1. STATEMENT OF THE BENEFITS TO BOTH CONSUMER AND TO THE PUBLIC EXPECTED FROM THE PROPOSED CHANGE**

Paracetamol 500 mg in combination with 5 mg phenylephrine or 5 mg phenylephrine hydrochloride per oral dose unit was introduced in 2006 as a replacement for the cough and cold medications on the market that contained pseudoephedrine 30 mg in combination with paracetamol 500 mg per solid dose unit. This was done to reduce the availability of precursor materials for the manufacture of the illicit drug methamphetamine, while still giving the benefit of a decongestant present in the formulation and retention of ease of OTC access. The underlying assumption was that there is no interaction between these two components which has now been demonstrated to not be the case. When this was done, it was a worldwide accepted standard to base this on the pharmacological similarity between the two decongestant compounds, despite no thorough safety or efficacy data being generated for the new combination of phenylephrine with paracetamol following the dosing recommended by the FDA monograph for OTC Nasal Decongestant Products (10 mg of phenylephrine every 4 hours to a maximum of 60 mg in 24 hours).

It has recently been discovered that a pharmacokinetic interaction where phenylephrine hydrochloride 10 mg in combination with paracetamol 1000 mg shows an approximate doubling of the phenylephrine plasma  $AUC_{0-\infty}$  and quadrupling of the  $C_{max}$  (Atkinson et al 2014, [REDACTED])

From the phenylephrine plasma concentration data collected [REDACTED] it is

apparent that increasing phenylephrine plasma concentrations is related to increased systolic and diastolic BP. The predicted blood pressure increase for different products containing 5-10 mg phenylephrine is presented in the table 2 below:

**Table 2.** Predicted BP increase for different products containing PE HCl

<b>Products containing Phenylephrine</b>	<b>Mean Change in Mean Arterial Pressure (mmHg)</b>	<b>Max Change in Mean Arterial Pressure (mmHg)</b>
Phenylephrine 10 mg alone	+4	+ 5- 6
Phenylephrine 10 mg + Paracetamol 1000 mg	+12	+19.5
Phenylephrine 5mg + Paracetamol 1000 mg	+6.6	+10

The table shows that the rise in BP for the modified product, Maxiclear PE 2.5 is relatively close to that of PE 10 mg alone whereas the PE C<sub>max</sub> values for the combination of Paracetamol 1000 mg plus PE 10 mg would be expected to result in much higher potential rises in BP for patients with co-existing disease states.

Clinical safety studies on PE have generally been conducted with young healthy volunteers, and more than likely the doubling of the PE plasma AUC, when taken in conjunction with paracetamol, would be expected to have minimal safety implications in that group. However, the same cannot be concluded for older patients, or those with already compromised cardiovascular systems including many who will also be undiagnosed or asymptomatic. Patients of all ages are likely to be affected by the observed increases in CNS AEs. For these reasons the move to substitute a 50% reduction in PE dose when supplied in conjunction with paracetamol, to replace the current marketed PE dose used in unscheduled category, seems an obvious move to reflect long standing single and daily dose guidelines.

So the key element here is that the effective dose of phenylephrine is altered by the combination such that the original assumption does not apply since without alteration of the phenylephrine dose, the phenylephrine exposure is double that of the FDA monograph (Atkinson et al 2014). However alteration of the phenylephrine dose when used in combination with paracetamol can restore the exposure of phenylephrine in line with the original OTC monograph.

**Mode of Action of the Individual Components of the Combination:**

**Paracetamol:**

Although the exact site and mechanism of analgesic action is not clearly defined, paracetamol appears to produce analgesia by elevation of the pain threshold.

**Phenylephrine hydrochloride:**

Phenylephrine hydrochloride is a sympathomimetic with direct effects on adrenergic receptors. It has mainly alpha-adrenergic activity. Its pressor activity is weaker than that of noradrenaline but of longer duration.

**2. POTENTIAL RISK OF HARM TO THE CONSUMER AS A RESULT OF THE PROPOSED CHANGE**

There is no expected risk of harm to the consumer as a result of the proposed changing of paracetamol 500 mg in combination with more than 2.5 mg phenylephrine per tablet/capsule/caplet and paracetamol 1000 mg in combination with more than 5 mg phenylephrine per sachet to Pharmacist Only. The proposed scheduling for paracetamol 500 mg in combination with 2.5 mg phenylephrine or less in packs containing more than 20 tablets, capsules or caplets and powders containing paracetamol 1000 mg in combination with 5 mg phenylephrine or less in packs containing more than 10 sachets to be Pharmacy Only and in packs containing 20 or less tablets, capsules or caplets and powders containing paracetamol 1000 mg in combination with 5 mg phenylephrine or less in packs containing 10 or fewer sachets to be General Sale is in line with the current scheduling for paracetamol.

**3. EASE OF SELF-DIAGNOSIS OR DIAGNOSIS BY A PHARMACIST FOR THE CONDITION INDICATED**

The symptoms of cold are easy enough to recognise – this generally includes sore throat, runny nose and congestion and cough (Jackson et al 1962, <http://www.webmd.com/cold-and-flu/cold-guide/flu-cold-symptoms>). These symptoms may also be present with influenza, although these are often more severe in nature and also include headache, fever and muscle pain (<http://www.webmd.com/cold-and-flu/cold-guide/flu-cold-symptoms>).

**4. RELEVANT COMPARATIVE DATA FOR LIKE COMPOUNDS**

Phenylephrine is a sympathomimetic amine. It is a selective  $\alpha$ -1 adrenergic receptor agonist. It is similar in structure to pseudoephedrine and phenylpropanolamine, however it is not able to be easily converted into methamphetamine like pseudoephedrine and does not have psychoactive properties like phenylpropanolamine. The main application for all three of these compounds was nasal decongestion (MCC - <http://www.medsafe.govt.nz/downloads/MCC32Phenylephrine.pdf>)

**5. LOCAL DATA OR SPECIAL CONSIDERATIONS RELATING TO NEW ZEALAND**

Obesity is a well-known risk factor for cardiovascular disease, and New Zealand has the third highest obesity rate in the world measured using BMI

([http://www.stats.govt.nz/browse\\_for\\_stats/snapshots-of-nz/nz-social-indicators/Home/Health/obesity.aspx](http://www.stats.govt.nz/browse_for_stats/snapshots-of-nz/nz-social-indicators/Home/Health/obesity.aspx)). Similarly, the general New Zealand population is aging, also a well-known risk factor for the development of cardiovascular complications (North & Sinclair 2012). There may be a number of these individuals who are obese and/or aging that have undiagnosed or asymptomatic cardiovascular disease that could potentially be exacerbated by the increase in blood pressure seen when the current dose of 10 mg phenylephrine is administered with 1000 mg paracetamol. These individuals may have a greater blood pressure response than what was predicted for healthy volunteers.

## 6. INTERACTIONS WITH OTHER MEDICINES

### Paracetamol

The following interactions have been noted [REDACTED]:

- anticoagulant drugs (e.g. warfarin): dosage may require reduction if paracetamol and anticoagulants are taken for a prolonged period of time
- antiepileptic medications: the likelihood of toxicity may be increased by the concomitant use of enzyme inducing agents
- metoclopramide, a medicine that increases gastric emptying may increase paracetamol absorption
- substances that decrease gastric emptying e.g. propantheline, antidepressants with anticholinergic properties may decrease paracetamol absorption
- narcotic analgesics e.g. chloramphenicol: paracetamol may increase chloramphenicol plasma concentrations
- hepatotoxic drugs or drugs that induce liver microsomal enzymes such as alcohol and anticonvulsant agents: the risk of paracetamol toxicity may be increased in patients receiving these drugs
- probenecid: may affect paracetamol excretion and plasma concentrations
- cholestyramine: reduces the absorption of paracetamol if given within 1 hour of paracetamol.
- isoniazid alone or combined with other drugs for tuberculosis: in patients receiving these drugs severe hepatotoxicity at therapeutic doses or moderate overdoses of paracetamol has been reported
- zidovudine and co-trimoxazole : severe hepatotoxicity has occurred after use of paracetamol in a patients taking these drugs.

### Phenylephrine hydrochloride:

The following interactions have been noted with

- sympathomimetics, vasodilators and beta-blockers
- monoamino oxidase inhibitors

## 7. CONTRAINDICATIONS AND PRECAUTIONS

### Contraindications:

Paracetamol and phenylephrine combination products are contraindicated for use:

- In patients with known hypersensitivity reaction to paracetamol, phenylephrine or any of the other ingredients in the respective formulations.
- In patients with active alcoholism as chronic excessive alcohol ingestion may predispose patients to paracetamol hepatotoxicity (due to the paracetamol component)
- In patients with active gastrointestinal bleeding, peptic ulceration or other stomach disorders
- During pregnancy or in patients planning to become pregnant
- During breastfeeding
- In patients with impaired liver function, renal function or cardiovascular disorders.
- In patients with eye disorders (mydriasis, acute angle closure glaucoma)
- In patients receiving or within two weeks stopping therapy with monoamine oxidase inhibitors because of the risk of hypertensive crisis.

**Precautions:**

- Paracetamol and phenylephrine combination products should not be taken with other products containing paracetamol and phenylephrine, unless under a doctor's instruction.
- No dose adjustment is required for older patients
- Nothing in the available information on phenylephrine and paracetamol suggests an increased or novel risk of genotoxicity or carcinogenicity with co-administration of phenylephrine and paracetamol compared to when administered alone.
- Paracetamol has been found to reduce birth weights when administered to pregnant mice throughout gestation.
- Phenylephrine has been found to significantly lower the number of ovum implantations in rabbits. However, this did not alter the incidence of pregnancy.
- Moderate doses of phenylephrine (3 mg/day or 1 mg/kg) to rabbits during the last trimester of pregnancy (from gestation day 22 through to labour) may cause "perinatal wastage", prematurity, premature labour and possible foetal abnormalities. The same dose of phenylephrine given during the first trimester (from gestation days 3 – 10) led to a decreased birth weight. Another study showed that phenylephrine was associated with aortic arch anomalies and ventricular septal defects in chick embryos.
- Paracetamol and phenylephrine combination products are recommended for use during pregnancy or for nursing mothers.
- Paracetamol and phenylephrine combination products should be used with caution, and at the lowest effective dose for the shortest duration, in patients with a history of gastrointestinal haemorrhage or a history of peptic ulcers since their condition may be exacerbated. It is contraindicated in patients with active gastrointestinal bleeding and in those with peptic ulcers and other stomach disorders.



- Caution is advised when prescribing paracetamol and phenylephrine combination products to patients with hypertension. Blood pressure should be monitored closely during initiation of treatment with these combination products and at regular intervals thereafter.
- As with other nasal decongestants which are sympathomimetic amines, such as pseudoephedrine and phenylpropanolamine, phenylephrine has the potential to cause hypertension and hypertensive crises.
- In the heart, the main effect of phenylephrine is reflex bradycardia secondary to increased arterial blood pressure. Bradycardia occurs after parenteral administration of usual therapeutic doses and may also result from overdosage. Therefore, patients with hypertension, stroke disease history, and other cardiovascular diseases are not encouraged to use phenylephrine as a self-medication of nasal congestion without consulting a doctor. At supra therapeutic doses, phenylephrine also acts on  $\beta$ -1 adrenergic receptors in the heart to produce a positive inotropic effect, but the drug does not appear to affect cardiac efficiency. Rarely, phenylephrine may increase the irritability of the heart, predisposing to arrhythmias such as ventricular tachycardia, but this occurs less often than with other antihistamines such as pseudoephedrine.
- Hypersensitivity reactions to paracetamol are known and can manifest in susceptible individuals as a rash that may be erythematous or urticarial or as more severe reactions with fever and necrotizing lesions in the skin and mucous membranes. Patients should be advised of the signs and symptoms of serious skin reactions and to consult their doctor at the first appearance of a skin rash or any other sign of hypersensitivity.
- Common phenylephrine side effects include nervousness, irritability, restlessness, dizziness, excitability and insomnia.

## 8. POSSIBLE RESISTANCE

Not applicable.

## 9. ADVERSE EVENTS – NATURE, FREQUENCY, ETC

A table outlining 28 adverse events to phenylephrine in 11 separate reports to Medsafe from 1 Jan 2000 to 1 July 2014 is presented below. No deaths have been reported.

**Table 3. Adverse events in relation to phenylephrine reported to Medsafe between 1 Jan 2000 and 1 July 2014.**

System Organ Class	MedDRA Reaction Term	Number of Reports
Eye disorders	Conjunctivitis	1
	Periorbital oedema	1
	Photophobia	1
Gastrointestinal disorders	Abdominal distension	1
	Nausea	1
	Tongue oedema	1
	Vomiting	2
General disorders and	Chest discomfort	1

administration site conditions	Chills	1
Immune system disorders	Anaphylactic reaction	2
Infections and infestations	Rhinitis	1
Nervous system disorders	Dizziness	2
	Headache	2
	Hyperkinesia	1
	Syncope	1
Psychiatric disorders	Abnormal dreams	1
	Anger	1
	Hallucination	1
Respiratory, thoracic and mediastinal disorders	Apnoea	1
	Dyspnoea	1

## 10. POTENTIAL FOR ABUSE OR MISUSE

Phenylephrine is highly unlikely to be misused or abused. It has no euphoric effect. 6 cases of dependence have been mentioned in a UK public assessment report (MHRA PL 16028/0114), but no information on these reported. While the structure of phenylephrine is highly similar to pseudoephedrine, it is much more difficult to convert phenylephrine to the illicit substance methamphetamine (MHRA PL 16028/0114).

Paracetamol is not able to be converted into a schedule 8 poison. Paracetamol is not an addictive substance, nor does it give an euphoric effect. Paracetamol is the most common agent responsible for accidental poisonous ingestions in young children (Starship 2010). Individuals with psychiatric disorders have also been known to overdose in deliberate attempts to self-harm. At the established therapeutic dosage level, paracetamol is unlikely to produce dependency or be misused or abused. However, there have been reports of accidental ingestion and overdose in children (Starship 2010) and deliberate self-harm by teenagers and adults (Starship 2010). Restriction of pack sizes and clear instructions minimise this risk. There is unlikely to be an increased risk attributable to paracetamol from this combination provided the same base rules apply as apply to paracetamol 500mg alone.

## CONCLUSION

Recent clinical findings have shown that the bioavailability of phenylephrine is doubled and the maximum plasma concentration effectively quadrupled when 10 mg is administered with 1000 mg of paracetamol in healthy volunteers. Blood pressure has been found to be significantly increased in healthy volunteers from baseline when 10 mg phenylephrine was administered with 1000 mg paracetamol. Therefore, having combinations that comprise of more than 2.5 mg phenylephrine in combination with 500 mg paracetamol per tablet, capsule or caplet and 1000 mg paracetamol in combination with more than 5 mg phenylephrine per sachet of powder as a Pharmacist Only medicine reduces the potential risk for adverse cardiovascular events that may result in susceptible individuals such as those who are overweight/obese and/or elderly and have concomitant undiagnosed or

asymptomatic cardiovascular conditions, as these individuals may have a greater blood pressure response.

## REFERENCES

The following four references that have been blanked out are clinical trials that have been made available to the Medicines Classification Committee. The fifth blanked out reference is an unpublished analysis carried out in-house, also made available to the MCC.

[Redacted reference text]

[Redacted reference text]

[Redacted reference text]

[Redacted reference text]

[Redacted reference text]

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**FDA.** 2006. Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Drug Products for Over-the-Counter Human Use; Amendment of Monograph for OTC Nasal Decongestant Drug Products. "Department of Health and Human Services". U.S Food and Drug Administration 71: 43359.

**Jackson G.G., Dowling, H.F., Muldoon, R.L.** (1962) VII. Present Concepts of the Common Cold. *Respiratory Diseases of Viral Etiology*, 52(6): 940 – 945.

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<http://www.medsafe.govt.nz/projects/B1/ADRSearch.asp>

[http://www.stats.govt.nz/browse\\_for\\_stats/snapshots-of-nz/nz-social-indicators/Home/Health/obesity.aspx](http://www.stats.govt.nz/browse_for_stats/snapshots-of-nz/nz-social-indicators/Home/Health/obesity.aspx)

<http://www.webmd.com/cold-and-flu/cold-guide/flu-cold-symptoms>

