MEDSAFE
NEW ZEALAND MEDICINES AND MEDICAL DEVICES SAFETY AUTHORITY
A BUSINESS UNIT OF THE MINISTRY OF HEALTH

Comments on Agenda Items for the 53rd meeting of the Medicines Classification Committee on Tuesday 5 May 2015

Public Consultation

Medsafe
April 2015

MINISTRY OF HEALTH
MANATU HAUORA

New Zealand Government

February 27, 2015

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Agenda for the 53rd Meeting of the Medicines Classification Committee

Dear Andrea,

Thank you for the opportunity to submit comments on the Agenda for the 53rd meeting of the Medicines Classification Committee. Te Arai BioFarma Ltd would like to comment on Agenda item 5.3 Ketoprofen for topical use and to support the up-scheduling of Ketoprofen for topical use to a Pharmacy-Only Medicine classification despite the known issue on the adverse skin reactions due to photosensitivity.

The reasons for this are outlined below.

- The Singapore Regulator, which is a Recognised Authority by Medsafe, has classified Fastum Gel 2.5% as "Pharmacy Only". This is despite the fact that according to WHO Singapore has significantly greater annual exposure to UV light than New Zealand, provided as Annex A.

- Some topical medicines classified as Pharmacy Only Medicine in New Zealand (Rheumon Gel – Etofenamate 50g and Thermo-Rheumon -Benzyl nicotinate/Etofenamate 100g) are known to cause photosensitivity or other serious skin related adverse reactions.

  A study useful for standardising relative risks but not absolute risks in a general population where risk minimisation measures are in place is provided as Annex B. The attached controlled study enrols patients with previous contact skin reactions and irradiates a patch of skin with a significant dose of UVA light. As such the study demonstrates a similar level of photosensitivity skin reactions between Ketoprofen and Etofenamate as well as Octocrylene sunscreen.

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- The Centre for Adverse Reactions Monitoring (CARM) of New Zealand have reported similar rates of skin reactions between Ketoprofen gel 2.5% and Diclofenac emulgel (on the market and approved as General Sale in New Zealand). The CARM report is provided as Annex C.

Product	Total adverse event reported to CARM (10 Yr period 2000 through 2010)	Skin related Adverse event reported to CARM (10 Yr period 2000 through 2010)	Packs per year*	2000-2010 patient exposure	Total adverse event rate (%)	Skin adverse event rate (%)	Serious skin adverse event rate
Voltaren	26	6	139,000	1,390,000	0.0019% (18.7 per million)	0.00043% (4.3 per million)	None reported
Oruvail	1	1	19,082	190,820	0.00052% (5.2 per million)	0.00052% (5.2 per million)	None reported

* Oruvail pack per year 2002 IMS sales data, 30g eq. packs. 11 years post launch. Voltaren 2009 IMS sales data, 50g eq. packs. (64k from 100g + packs, 75k from 20 and 50g packs). Assumes IMS sales year represents average sales over 10 year period.

- Risk minimization measures to minimize skin adverse reactions will be applied:

  - Since 1994 New Zealand Health Protection Agency has successfully run a national sun protection campaign originally under the banner “SLIP. SLOP. SLAP”. This has since been expanded to “SLIP. SLOP. SLAP. WRAP”. The logo for this national sun protection campaign could easily be incorporated on the packaging, provided as Annex D.
  - Warnings on sun exposure can be included on the packaging and product information, as well as warnings on adverse skin reactions when topical Ketoprofen is used together with Octocrylene.
  - The maximum pack size to be sold Pharmacy-Only is 50g; and, topical Ketoprofen should be used for a maximum of ten (10) days, after that referral to a medical practitioner will be requested.

Te Arai BioFarma Ltd considers that Ketoprofen for topical use is in line with the requirements for a classification as Pharmacy-Only in New Zealand.

Kind Regards,

Lance Gravatt
Chairman
Te Arai BioFarma Ltd

Annex A

New Zealand (Wellington)	42°S	7	7	5	3	1	1	1	2	4	6	7	8
Singapore (Singapore)	1°N	11	12	13	13	11	11	11	11	12	12	11	10

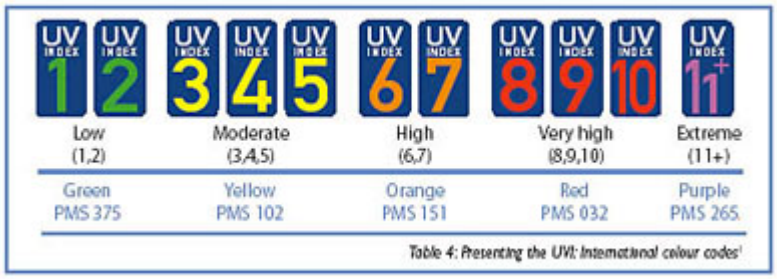

Table 4: Presenting the UVI: International colour codes[1]

Reference:

http://www.who.int/uv/intersunprogramme/activities/uv_index/en/index3.html

BJD
British Journal of Dermatology

A European multicentre photopatch test study

The European Multicentre Photopatch Test Study (EMCPPTS) Taskforce[1]

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Summary

Background The two most common agent groups currently responsible for photoallergic contact dermatitis (PACD) are organic ultraviolet (UV) absorbers in sunscreens and topical nonsteroidal anti-inflammatory drugs (NSAIDs). However, availability of information on the photoallergenic potential of these agents is scarce.

Objectives To obtain current information on the frequency of PACD to 19 organic UV absorbers and five topical NSAIDs, including newer agents, in common usage in Europe.

Methods A prospective, multicentre photopatch test study was conducted with 1031 patients attending for investigation of suspected PACD in 30 centres across 12 European countries.

Results A total of 346 PACD reactions in 200 (19·4%) subjects occurred. PACD was most commonly caused by the topical NSAIDs, ketoprofen (128 subjects) and etofenamate (59 subjects). Of the organic UV absorbers, octocrylene, benzophenone-3 and butyl methoxydibenzoylmethane most frequently elicited PACD. The 'newer' organic sunscreen absorbers rarely led to PACD. There appeared to be an association between the agents ketoprofen, octocrylene and benzophenone-3, with several subjects developing PACD to two or all three agents concomitantly. Allergic contact dermatitis (ACD) was less commonly observed than PACD, comprising 55 reactions in 47 (5%) subjects. Irritant reactions and photoaugmentation and photoinhibition of ACD occurred infrequently.

Conclusions The European multicentre photopatch test study has provided current information on the relative frequency of PACD to common photoallergens. Such data will be of value when deciding on which agents to include in a future European 'baseline' photopatch test series.

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Accepted for publication
11 January 2012

Funding sources
Chemotechnique Diagnostics, Vellinge, Sweden and L'Oréal Research and Innovation, Clichy, France.

Conflicts of interest
None declared.

[1]A list of the members of the EMCPPTS Taskforce and their affiliations is given in Appendix.

DOI 10.1111/j.1365-2133.2012.10857.x

Photoallergic contact dermatitis (PACD) is the delayed-type hypersensitivity reaction which occurs when an exogenous agent (photoallergen) is applied to the skin and subsequently exposed to ultraviolet (UV) and/or visible radiation. Historically, several agents have been identified as photoallergens, some of which have subsequently been removed from the European marketplace. Currently, the two most common agent groups are organic UV absorbers used in sunscreens and topical nonsteroidal anti-inflammatory drugs (NSAIDs).[1] The incidence of PACD is unknown, but it is thought to be uncommon with frequencies of 2–10% reported among patients referred for investigation of a photoexposed-site dermatosis.[2–4] The investigation of choice for diagnosing PACD is photopatch testing (PPT), for which a European consensus methodology has existed for several years.[5] However, in contrast to conventional patch testing, for which several national and international 'baseline' series of allergens exist, currently no European 'baseline' PPT series has been agreed on. This is in part because limited data exist on the current most common photoallergens in Europe.

In 2007, a group of interested clinicians met in Amsterdam under the auspices of the European Society for Photodermatology and the European Society of Contact Dermatitis with the aim of setting up a European multicentre photopatch test study (EMCPPTS).

The primary objective of the study was to determine the frequency of PACD to 19 organic UV absorbers and five topical NSAIDs in common usage in Europe among patients presenting for investigation of suspected PACD using a standardized PPT technique.

Materials and methods

Several photobiology and contact dermatitis units across Europe were invited to participate. At the initial meeting, there was agreement that the total target number of subjects would

be > 1000 over a 1-year period. This figure was not generated from a formal statistical sample size calculation, but based on consensus that it would provide a clinically valuable estimate of the frequency of PACD, while being practically achievable over the timescale intended.

Due to heterogeneous legislation and its interpretation across different European countries, some investigators had to seek and obtain ethical approval, whereas others did not. The latter group considered the PPT investigation as part of routine clinical care. The inclusion criteria specified that subjects must be aged 18 years or older and have sufficient understanding to give written informed consent. Those included had at least one of the following four indications for performing PPT: (i) an exposed-site dermatitis during summer months; (ii) any exposed-site dermatitis; (iii) history of a sunscreen reaction; or (iv) history of a topical NSAID skin reaction.

Exclusion criteria were: (i) potent topical steroid applied to the photopatch test site on the back in the 5 days prior to PPT; (ii) skin disease activity on the back which was too active to allow PPT; and (iii) subjects prescribed systemic immunosuppressant medication (i.e. prednisolone, methotrexate, azathioprine, ciclosporin). In addition, a relative contraindication was any patient taking photoactive medicine (e.g. thiazides, fluoroquinolones, NSAIDs, quinine) at the discretion of the clinician.

PPT was conducted according to the European consensus methodology as described previously.[5] In brief, the test agents were applied to the skin of the back and removed at 24 or 48 h, depending on the set-up at each centre. One set was then irradiated with 5 J cm^{-2} UVA (or less if UVA minimal erythemal dose testing revealed objective photosensitivity[6]) while the other set was covered with a UV-impermeable material. Readings of the test site could then be made at five different time points: preirradiation, immediately postirradiation, 24 h postirradiation, 48 h postirradiation and 72 h postirradiation or later. However, the reading made at 48 h postirradiation was considered the key time point and subsequent data analysis focused on this.[3] Prior to any subject recruitment, all participating centres were asked to send their UVA meters via post to the coordinating centre in Dundee for calibration. This laboratory is International Organisation for Standardisation (ISO) 9001 registered and U.K. Accreditation Service (UKAS) accredited. The meters were tested using a bank of 100-W UVA lamps and calibrated using a Bentham model DM150 spectroradiometer (Bentham Instruments Ltd, Reading, U.K.) with calibration traceable to the U.K. National Physical Laboratory.

The photopatch test series of 19 organic UV absorbers and five topical NSAIDs with the concentrations used are given in Table 1. The 24 agents were donated by Chemotechnique Diagnostics Ltd (Vellinge, Sweden). The 19 UV absorbers are all in common usage and among the 26 sunscreening agents currently permitted for use in cosmetic products by the European Commission.[7] All UV absorbers were tested at a concentration of 10%, except benzophenone-4, which was used at a 2% concentration due to the irritant potential of higher concentrations discovered during a pilot irritancy study.[8] The concentrations of the topical NSAIDs used were chosen after consensus was reached by several members at the initiation meeting who had expertise in testing with these agents. All agents were prepared in petrolatum except terephthalylidene dicamphor sulfonic acid which was prepared in water, as it has a low pH which requires the addition of a neutralizing agent to prevent irritant reactions.

Table 1 The European multicentre photopatch test study test agents, with chemical abstracts service (CAS) numbers and concentrations

Test agent[a]	CAS number	Concentration (%)
Butyl methoxydibenzoylmethane	70356-09-1	10
Homosalate	8045-71-4	10
4-Methylbenzylidene camphor	36861-47-9	10
Benzophenone-3	131-57-7	10
Ethylhexyl methoxycinnamate	5466-77-3	10
Phenylbenzimidazole sulfonic acid	27503-81-7	10
Benzophenone-4	4065-45-6	2
Drometrizole trisiloxane	155633-54-8	10
Octocrylene	6197-30-4	10
Ethylhexyl salicylate	118-60-5	10
Ethylhexyl triazone	88122-99-0	10
Isoamyl-*p*-methoxycinnamate	71617-10-2	10
Terephthalylidene dicamphor sulfonic acid	90457-82-2	10
bis-Ethylhexyloxyphenol methoxyphenyl triazine	187393-00-6	10
Methylene *bis*-benzotriazolyl tetramethylbutylphenol	103597-45-1	10
Diethylamino hydroxybenzoyl hexyl benzoate	302776-68-7	10
Disodium phenyl dibenzimidazole tetrasulfonate	180898-37-7	10
Diethylhexyl butamido triazone	154702-15-5	10
Polysilicone-15	207574-74-1	10
Ketoprofen	22071-15-4	1
Etofenamate	30544-47-9	2
Piroxicam	36322-90-4	1
Diclofenac	15307-79-6	5
Ibuprofen	15687-27-1	5
Control (Pet)	n/a	n/a

[a]International Nomenclature of Cosmetic Ingredients (INCI) name (for organic ultraviolet absorbers). Pet, petrolatum; n/a, not applicable.

All PPT reactions were graded using the International Contact Dermatitis Research Group (ICDRG) system.[9] Investigators were asked to assign relevance to any positive reactions seen whenever possible using the COADEX system.[10] This classifies positive reactions as follows: C, current relevance; O, old/past relevance; A, an active sensitization reaction; D, unknown relevance; E, history of exposure but not resulting in dermatitis; X, cross-reaction with another test agent. A single-sided A4-size paper proforma was used to record anonymous data for each subject (Appendix S1; see Supporting information).

The study proforma allowed space for inclusion of up to three of a subject's 'own agents' to be tested 'as is', e.g. commercial sunscreens. When completed, each proforma was faxed or posted to the coordinating centre in Dundee. The information included on all proformas received was entered into a secure database for subsequent data analysis.

Results

When using the above PPT methodology and ICDRG reaction grading system, interpretation allows six possible reaction patterns to be determined, as previously described.[3] These are PACD, allergic contact dermatitis (ACD), photoaugmentation of ACD, photoinhibition of ACD, irritant response (IR) and negative response. In the present study, all '+' ICDRG reactions were discounted for the purpose of data analysis.

Baseline data

A total of 1031 subjects were recruited, of whom 715 (69·4%) were female. The median age of subjects was 46 years (range 18–92). Regarding photopatch application time, this was 24 h in 679 (65·9%) subjects and 48 h in 347 (33·7%), with no duration specified in five subjects. The dose of UVA used for irradiation was 5 J cm^{-2} in 977 (94·8%) subjects, with the remaining 54 subjects receiving < 5 J cm^{-2}.

Subjects were recruited from 30 centres across 12 European countries. The number of subjects recruited by each centre is given in Figure 1 which shows that two U.K. centres accounted for 439 (42·6%) of the 1031 subjects recruited. The recruitment period had to be extended from 12 to 32 months (August 2008 to February 2011). One factor that contributed to the delay in subject recruitment at some centres was the completion of paperwork required to comply with the EU clinical trials directive.[11]

Photoallergic contact dermatitis reactions

A total of 346 PACD reactions in 200 subjects were recorded. Therefore, 19·4% of subjects had at least one PACD reaction, a frequency higher than in many previous studies. There was great variation in the frequency of PACD at each centre, ranging from 0% to 90·9% of subjects investigated (Appendix S2; see Supporting information). The number of PACD reactions recorded for each agent, with the corresponding ICDRG grade of the reaction in the irradiated set is given in Table 2. Of the 346 PACD reactions, 343 were assigned COADEX relevance, as follows: C = 152; O = 38; A = 1; D = 110; E = 3; X = 39 (Appendix S3; see Supporting information). The number of PACD reactions to ketoprofen, etofenamate, octocrylene and benzophenone-3 were high enough to allow analysis of PACD rates to each agent in each country (Appendix S4; see Supporting information). If reactions to NSAIDs were excluded, there were 148 PACD reactions in 95 subjects to the 19 organic UV absorbers, giving a lower PACD rate of 9·2%.

The frequency of PACD appeared to vary with duration of patch application. Of the 679 subjects who had patches applied for 24 h, 94 (13·8%) had at least one PACD reaction, whereas of the 347 subjects who had patches applied for 48 h, 105 (30·2%) had at least one PACD reaction. In the case of gender, of the 715 women recruited, 118 (16·5%) had at least one PACD reaction, compared with 82 (26·2%) of the 313 male subjects. The effect of age on the frequency of PACD was analysed by grouping subjects into 10-year blocks, as given in Table 3. After the age group 28–37 years, the frequency of PACD gradually decreased with age, except among subjects aged 78 years and older.

The frequency of PACD by diagnosis is shown in Table 4. As regards the 54 subjects in whom a dose < 5 J cm^{-2} was used for irradiation, the median dose used was 2·5 J cm^{-2} (range 0·25–4) and nine (16·7%) had at least one PACD reaction. When the indication for testing was examined, subjects who gave a history of reacting to a sunscreen or topical NSAID had higher rates of PACD than those with an exposed-site dermatitis or dermatitis in summer months (Table 5). Further analysis showed that of the 139 subjects with a history of reacting to a topical NSAID, 97 (69·8%) had at least one PACD reaction to one of the five NSAID test agents compared with 164 (15·9%) subjects of the total 1031 subjects recruited.

There appeared to be an association between PACD reactions to the three agents, ketoprofen, benzophenone-3 and octocryl-

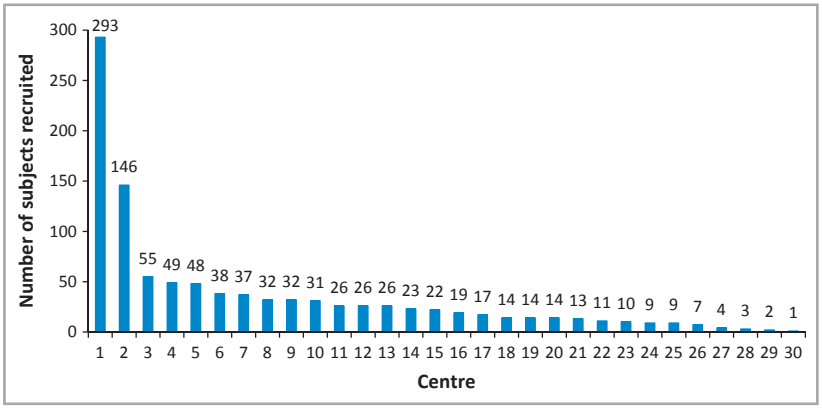

Fig 1. Recruitment of subjects in the European multicentre photopatch test study by centre (centres 1 and 2 were in the U.K.).

Table 2 Photoallergic contact dermatitis (PACD) reactions to the 19 organic ultraviolet (UV) absorbers and five topical nonsteroidal anti-inflammatory drugs in the European multicentre photopatch test study at 48 h postirradiation, with International Contact Dermatitis Research Group (ICDRG) grading of reactions in the irradiated set of test agents

Test agent[a]	Number of subjects with PACD reaction	ICDRG grade of PACD reaction in irradiated set		
		+	++	+++
Ketoprofen	128	23	65	40
Etofenamate	59	32	24	3
Octocrylene	41	11	19	11
Benzophenone-3	37	14	18	5
Butyl methoxydibenzoylmethane	18	10	6	2
Isoamyl-*p*-methoxycinnamate	10	4	6	0
Ethylhexyl methoxycinnamate	7	3	3	1
Methylene *bis*-benzotriazolyl tetramethylbutylphenol	5	5	0	0
Piroxicam	5	4	1	0
Terephthalylidene dicamphor sulfonic acid	4	2	2	0
Diethylamino hydroxybenzoyl hexyl benzoate	4	2	2	0
Ibuprofen	4	3	1	0
4-Methylbenzylidene camphor	3	1	2	0
Benzophenone-4	3	1	2	0
Ethylhexyl triazone	3	3	0	0
bis-Ethylhexyloxyphenol methoxyphenyl triazine	3	1	1	1
Disodium phenyl dibenzimidazole tetrasulfonate	3	2	1	0
Ethylhexyl salicylate	2	2	0	0
Diclofenac	2	1	1	0
Homosalate	1	1	0	0
Drometrizole trisiloxane	1	0	1	0
Polysilicone-15	1	1	0	0
Phenylbenzimidazole sulfonic acid	0	0	0	0
Diethylhexyl butamido triazone	0	0	0	0
Control (Pet)	2	2	0	0
Total	346	128	155	63

[a]International Nomenclature of Cosmetic Ingredients (INCI) name (for organic UV absorbers). Pet, petrolatum.

Table 3 Frequency of photoallergic contact dermatitis (PACD) reactions by age group

Subject age (years)	Total number of subjects	Subjects with at least 1 PACD reaction	
		n	%
18–27	117	20	17·1
28–37	191	45	23·6
38–47	243	53	21·8
48–57	205	39	19
58–67	177	25	14·1
68–77	80	11	13·8
78–87	17	6	35·3
88–97	1	1	100

Table 4 Frequency of photoallergic contact dermatitis (PACD) reactions by diagnosis

Diagnosis	Total number of subjects	Subjects with at least 1 PACD reaction	
		n	%
Atopic dermatitis	69	9	13·0
CAD	31	6	19·4
PLE	190	25	13·1
Other	393	80	20·4
Undiagnosed	343	75	21·9

CAD, chronic actinic dermatitis; PLE, polymorphic light eruption.

Table 5 Indication for testing and frequency of photoallergic contact dermatitis (PACD)

Indication for testing	Total number of subjects	Subjects with at least 1 PACD reaction	
		n	%
Exposed-site dermatitis in summer	517	83	16·1
Any exposed-site dermatitis	308	27	8·8
History of sunscreen reaction	226	63	27·9
History of NSAID reaction	139	97	69·8

NSAID, nonsteroidal anti-inflammatory drug.

ene, as given in Table 6. Further analysis of COADEX relevance in subjects who reacted to two or all three of these agents, showed that ketoprofen was commonly assigned current or old relevance with octocrylene and/or benzophenone-3 assigned as cross-reactions (Appendix S5; see Supporting information).

Other reaction patterns

In comparison to PACD, ACD was much less frequent, with a total of 55 reactions recorded in 47 (4·6%) subjects. Nine of the 24 test agents did not lead to any ACD reactions. The number of ACD reactions reported for the remaining 15 agents, with corresponding ICDRG grade of reaction are given in Table 7. As with PACD reactions, most ACD reactions were assigned current or unknown relevance. Photoaugmentation and photoinhibition of ACD were relatively uncommon reaction patterns, with only 21 reactions in 18 (1·7%) subjects and 14 reactions in 11 (1·1%) subjects, respectively. Similarly,

Table 6 The association of photoallergic contact dermatitis (PACD) reactions between ketoprofen, octocrylene and benzophenone-3 in subjects

Agent or combination of agents	Number of subjects with positive PACD reaction to agent(s)
Ketoprofen	128
Octocrylene	41
Benzophenone-3	37
Octocrylene and ketoprofen	34
Octocrylene and benzophenone-3	18
Ketoprofen and benzophenone-3	22
All three agents	15

Table 7 Allergic contact dermatitis (ACD) reactions to 15 organic ultraviolet (UV) absorbers and topical nonsteroidal anti-inflammatory drugs in the European multicentre photopatch test study at 48 h postirradiation, with International Contact Dermatitis Research Group (ICDRG) grading of reactions recorded

Test agent[a]	Number of subjects with ACD reaction	ICDRG grade of ACD reaction		
		+	++	+++
Methylene *bis*-benzotriazolyl tetramethylbutylphenol	11	8	3	0
Etofenamate	10	3	6	1
Octocrylene	7	4	3	0
Benzophenone-3	6	6	0	0
4-Methylbenzylidene camphor	4	4	0	0
Terephthalylidene dicamphor sulfonic acid	4	4	0	0
Butyl methoxydibenzoylmethane	3	2	1	0
Ethylhexyl methoxycinnamate	2	2	0	0
Isoamyl-*p*-methoxycinnamate	2	2	0	0
Ethylhexyl salicylate	1	1	0	0
bis-Ethylhexyloxyphenol methoxyphenyl triazine	1	1	0	0
Diethylamino hydroxybenzoyl hexyl benzoate	1	0	0	1
Disodium phenyl dibenzimidazole tetrasulfonate	1	1	0	0
Piroxicam	1	0	1	0
Ibuprofen	1	1	0	0
Totals	55	39	14	2

[a]International Nomenclature of Cosmetic Ingredients (INCI) name (for organic UV absorbers).

irritant reactions were rare, with only seven reactions in six (0·6%) subjects observed.

Testing to 'own' agents

A total of 347 of 1031 subjects had at least one 'own' agent tested in addition to the 24 test agents. For analysis, these were grouped into three main categories: (i) sunscreens 'as is' or other UV absorbers; (ii) topical NSAIDs; and (iii) 'other' agents (which included systemic medications and miscellaneous agents). A total of 48 PACD reactions in 48 (13·8%) subjects were recorded 48 h postirradiation, as given in Table 8. Eleven sunscreen reactions were assigned current relevance, with 15 assigned as unknown. A total of 46 ACD reactions in 40 (3·9%) subjects were recorded to additional 'own' agents 48 h postirradiation, 33 of which were to sunscreens, 13 to 'other agents' and zero to topical NSAIDs.

Table 8 Photoallergic contact dermatitis (PACD) reactions to additional 'own' agents at 48 h postirradiation with International Contact Dermatitis Research Group (ICDRG) gradings in the irradiated set

Agent category	Total number of reactions	ICDRG grade of PACD reaction in irradiated set		
		+	++	+++
Sunscreen/UV absorber	30	28	2	0
NSAID	8	2	0	6
Other	10	5	5	0

UV, ultraviolet; NSAID, nonsteroidal anti-inflammatory drugs.

Discussion

The EMCPPTS was conducted to generate a clearer picture of which agents currently in use in this area most frequently led to PACD.

Ketoprofen led to PACD in the greatest number of subjects, which suggests it may be a potent photoallergen, as has been previously reported.[12,13] The finding of likely cross-reaction in subjects between ketoprofen and benzophenone-3 has been previously reported, and can be explained by the benzophenone-like structure of ketoprofen.[14] However, ketoprofen and octocrylene PACD also appear associated, but this finding cannot be as easily explained by close structural similarity. This association has stimulated experimental work investigating possible molecular mechanisms for octocrylene allergenicity.[15] Although benzophenone-3 is declining in use, octocrylene use in sunscreens is increasing over time as it is effective at stabilizing butyl methoxydibenzoylmethane.[16]

In 2009, concerns about interactions with octocrylene led regulatory authorities in France to suspend all marketing authorizations for topical ketoprofen. This in turn led to a risk–benefit analysis by the European Medicines Agency. Although a 'positive benefit balance' was given, it can now be prescribed only by clinicians, and patients are given more warnings about the risk of developing PACD.[17] The findings of the EMCPPTS appear to confirm recent reports on the association between octocrylene and ketoprofen.[15,18] Such findings will be of concern to sunscreen manufacturers, whose octocrylene-containing sunscreens may lead to PACD in individuals who have been previously sensitized to ketoprofen. It appears

that ketoprofen may belong to a category of potent photoallergens such as tetrachlorosalicylanilide and carprofen.[19,20] In the case of both these agents, it was only after the agent was marketed that frequent episodes of photoallergy arose. The fact that agents like ketoprofen continue to emerge onto the marketplace questions whether current preclinical screening methods for detecting PACD are adequate.

The agent leading to PACD in the second largest number of subjects was the topical NSAID etofenamate. This anthranilic acid derivative is not available in the U.K., but is often used in Mediterranean countries. There are relatively few reports of ACD and PACD to etofenamate, but these results confirm it has photoallergenic potential.[21] Most etofenamate PACD reactions were of unknown relevance and interestingly some PACD reactions to etofenamate were recorded from U.K. centres. Our observations of etofenamate reactions in Dundee led us to hypothesize that a significant number may be due to phototoxicity, rather than PACD (Fig. 2).

The UV absorbers most commonly leading to PACD were octocrylene and benzophenone-3. As discussed above, many subjects may have developed cross-reactions to ketoprofen. However, they appear to have an inherent photoallergenic potential of their own. The high rates of PACD to butyl methoxydibenzoylmethane are likely to be at least partly due to its current high levels of usage within sunscreen preparations.[16] However, its role as the most important UVA absorber in sunscreens is likely to outweigh the relatively low risk of PACD and ACD for manufacturers.

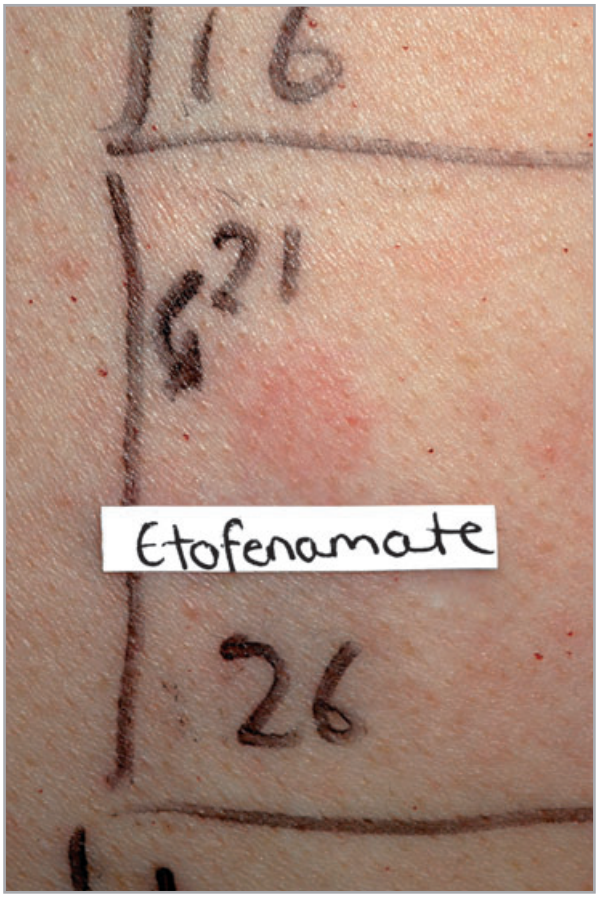

Fig 2. Close-up of etofenamate reaction at 24 h post irradiation in irradiated set, displaying '+' International Contact Dermatitis Research Group grade reaction.

Analysis of the four agents most commonly leading to PACD suggests that PACD to ketoprofen, octocrylene and benzophenone-3 may be most common in Italy, France, Belgium and Spain. It is possible this is due to regional availability and usage pattern differences, but as above, differences in subject recruitment mean that such interpretation can only be made cautiously.

The agent most commonly leading to ACD was methylene *bis*-benzotriazolyl tetramethylbutylphenol (Tinosorb M®; BASF, Ludwigshafen, Germany). This widely used UVB + UVA absorber is formulated as microfine nanoparticles, which require addition of the surfactant decyl glucoside. In the pilot irritancy study, it led to more positive reactions than all other agents except benzophenone-4.[8] A subsequent case of ACD to methylene *bis*-benzotriazolyl tetramethylbutylphenol has been reported, which attributed the problem to the decyl glucoside within it.[22]

It is not possible to explain the apparent difference in frequency of PACD between male and female subjects. Certain previous studies have actually reported higher rates of ACD in female subjects, but this was thought to reflect higher levels of exposure to certain allergens, such as nickel in jewellery and fragrances in cosmetics.[23,24]

When analysed by diagnosis, the rates of PACD appear higher in those with chronic actinic dermatitis (CAD) than either polymorphous light eruption or atopic dermatitis, but small numbers make firm conclusions difficult. It is known that patients with CAD have to use sunscreens more frequently than other groups and have a higher tendency to develop ACD and PACD to agents.[25,26] The inclusion of 54 subjects in whom a UVA dose of < 5 J cm^{-2} had to be used highlights that if PPT is performed correctly, members of this group of photosensitive subjects can be still be investigated.

When indications for testing were analysed, those with a history of reacting to a sunscreen or topical NSAID had a high frequency of PACD reactions, which confirms the importance of PPT as an investigation in these subjects. However, the less obvious indications of any exposed-site dermatitis or an exposed-site dermatitis in the summer months, should not be overlooked in patients presenting to the clinic.

Comparison of the EMCPPTS with the 2006 U.K. study by Bryden *et al.*,[3] which used the same methodology in a similar patient group, highlighted two different outcomes. Firstly, PACD rates in the EMCPPTS were much higher and, secondly, ACD rates did not match PACD rates. These differences are likely due to the inclusion of NSAIDs in the EMCPPTS and the routine inclusion of an 'as is' sunscreen in the 2006 study.[3] At that time obtaining pure forms of some test agents was not possible so as a surrogate the investigators used a commercial

SPF 60 sunscreen 'as is', which contained two such agents (terephthalylidene dicamphor sulfonic acid and drometrizole trisiloxane) for PPT. A large number of ACD and PACD reactions to this commercial sunscreen were seen, but their relevance could rarely be established.

Additionally, the 2006 study incorporated only one of the nine 'new' UV absorbers used in the EMCPPTS, ethylhexyl triazone. One of the most important findings in the present study is that all nine of the newer, larger-molecular-weight UV absorbers tested in pure form in the EMCPPTS led to PACD infrequently. This makes biological sense, as these larger molecules should penetrate less into the stratum corneum to elicit ACD and PACD.

The low rates of photoaugmentation and photoinhibition of ACD are in keeping with the 2006 study, but again serve to remind clinicians of the possibility of false positive and negative reactions when conducting PPT.[3,27] Irritant reactions were also rarely seen which confirms the finding of the pilot irritancy study that most organic UV absorbers can be photopatch tested at a concentration of 10%.[8]

There are some limitations to the study. The EMCPPTS was performed in subjects attending clinicians with suspected PACD. As a result, the frequency of PACD reported will be higher than that occurring in the European population as a whole. On a similar theme, the small numbers of subjects in certain analysed subgroups (e.g. by diagnosis) means that caution must be exercised when interpreting and extrapolating apparent patterns. The multicentre methodology of the study meant that differences in subject selection for recruitment occurred. Such differences will probably have largely accounted for the variation observed in rates of PACD between centres. Similar selection differences will also have contributed to the apparent variation in rates of PACD seen between subjects who had patches applied for 24 h (often from photobiology units) and those applied for 48 h (often from contact dermatitis units). A further limitation is that there was no accurate quantitative denominator data available in the form of the number of subjects exposed to each test agent. Therefore, for agents that led to few PACD reactions, this may reflect limited exposure rather than a low photoallergenic potential. Likewise, agents with many PACD reactions may reflect high usage, rather than a high photoallergenic potential.

In conclusion, the EMCPPTS has provided new information on the relative frequency of PACD in this selected patient group and the main photoallergens implicated. The study has also reinforced the important place of PPT, when performed according to the European consensus methodology, as an investigation in cases of possible PACD presenting to the clinician. The results obtained will be of value to interested parties in the future when deciding which agents to include in a new and up-to-date European 'baseline' photopatch test series. It also serves as a benchmark for tracking trends in PACD over time and similar studies will need to be repeated periodically to ensure agents included in photopatch test series continue to be of relevance.

What's already known about this topic?

- Organic sunscreen absorbers and topical nonsteroidal anti-inflammatory drugs (NSAIDs) are the two agent groups most commonly leading to photoallergic contact dermatitis (PACD).
- The frequency of PACD to agents in these two groups has been reported in previous multicentre studies.
- The availability to the public of agents in these two groups changes over time, as new products emerge onto the marketplace.
- Photopatch testing series require periodic updating and, currently, no European 'baseline' photopatch test series exists.

What does this study add?

- Updated information on the relative frequency of PACD to 19 organic sunscreen absorbers, including newer agents, and five topical NSAIDs currently used in Europe.

Acknowledgments

All contributors would like to thank the faculty staff members at recruiting centres for their assistance with the project. We wish to thank Bo Niklasson of Chemotechnique Diagnostics Ltd, Vellinge, Sweden for donating the test agents. We would like to thank the Health Informatics Centre (HIC) personnel at the University of Dundee, U.K. for data entry and extraction. We would also like to thank Professor Harry Moseley and Ms Lynn Fullerton of the Photobiology Unit in Dundee, U.K. for the calibration of UV meters and Drs Robert Dawe and Sally Ibbotson for their help in appraising the manuscript.

References

1 Kerr A, Ferguson J. Photoallergic contact dermatitis. *Photodermatol Photoimmunol Photomed* 2010; **26**:56–65.
2 Bell HK, Rhodes LE. Photopatch testing in photosensitive patients. *Br J Dermatol* 2000; **142**:589–90.
3 Bryden AM, Moseley H, Ibbotson SH *et al.* Photopatch testing of 1155 patients: results of the U.K. multicentre photopatch study group. *Br J Dermatol* 2006; **155**:737–47.
4 Darvay A, White IR, Rycroft RJ *et al.* Photoallergic contact dermatitis is uncommon. *Br J Dermatol* 2001; **145**:597–601.
5 Bruynzeel DP, Ferguson J, Andersen K *et al.* Photopatch testing: a consensus methodology for Europe. *J Eur Acad Dermatol Venereol* 2004; **18**:679–82.
6 British Photodermatology Group. Photopatch testing-methods and indications. *Br J Dermatol* 1997; **136**:371–6.
7 European Commission. List of permitted UV filters which cosmetic products may contain. Annex VII (Part 1). EC Health and Consumers, Cosmetic Ingredients and Substances. Available at: http://ec.europa.eu/consumers/cosmetics/cosing/index.cfm?fuseaction=search.results&annex_v1 = VII&search (last accessed 2 February 2012).

8 Kerr AC, Niklasson B, Dawe RS *et al.* A double-blind, randomized assessment of the irritant potential of sunscreen chemical dilutions used in photopatch testing. *Contact Dermatitis* 2009; **60**:203–9.
9 Wahlberg JE. Patchtesting. In: *Textbook of Contact Dermatitis* (Rycroft R, Menne T, Frosch P, Lepoittevin JL, eds), 3rd edn. Berlin: Springer-Verlag, 2001; 939–68.
10 Bourke J, Coulson I, English J. British Association of Dermatologists' Guidelines for care of contact dermatitis. *Br J Dermatol* 2001; **145**:877–85.
11 European Commission. The implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use. EC Directive 2001/20/EC. Available at: http://ec.europa.eu/health/human-use/clinical-trials/index_en.htm (last accessed 2 February 2012).
12 Hindsen M, Isaksson M, Persson L *et al.* Photoallergic contact dermatitis from ketoprofen induced by drug-contaminated personal objects. *J Am Acad Dermatol* 2004; **50**:215–19.
13 Diaz RL, Gardeazabal J, Manrique P *et al.* Greater allergenicity of topical ketoprofen in contact dermatitis confirmed by use. *Contact Dermatitis* 2006; **54**:239–43.
14 Le Coz CJ, Bottlaender A, Scrivener JN *et al.* Photocontact dermatitis from ketoprofen and tiaprofenic acid: cross-reactivity study in 12 consecutive patients. *Contact Dermatitis* 1998; **38**:245–52.
15 Karlsson I, Vanden Broecke K, Martensson J *et al.* Clinical and experimental studies of octocrylene's allergenic potency. *Contact Dermatitis* 2011; **64**:343–52.
16 Kerr AC. A survey of the availability of sunscreen filters in the U.K. *Clin Exp Dermatol* 2011; **36**:541–3.
17 European Medicines Agency. Ketoprofen topical. Outcome of a procedure under article 107 of Directive 2001/83/EC. Available at: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/referrals/Ketoprofen_topical/human_referral_000238.jsp&murl=menus/regulations/regulations.jsp&mid=WC0b01ac0580024e99 (last accessed 2 February 2012).
18 Avenel-Audran M, Dutartre H, Goossens A *et al.* Octocrylene, an emerging photoallergen. *Arch Dermatol* 2010; **146**:753–7.
19 Wilkinson DS. Photodermatitis due to tetrachlorsalicylanilide. *Br J Dermatol* 1961; **73**:213–19.
20 Kerr AC, Muller F, Ferguson J *et al.* Occupational carprofen photoallergic contact dermatitis. *Br J Dermatol* 2008; **159**:1303–8.
21 Goday Bujan JJ, Perez Varela L, Pineyro Molina F *et al.* Allergic and photoallergic contact dermatitis from etofenamate: study of 14 cases. *Contact Dermatitis* 2009; **61**:118–20.
22 Andrade P, Goncalo M, Figueiredo A. Allergic contact dermatitis to decyl glucoside in Tinosorb M. *Contact Dermatitis* 2010; **62**:119–20.
23 Leyden JJ, Kligman AM. Allergic contact dermatitis: sex differences. *Contact Dermatitis* 1977; **3**:333–6.
24 Rees JL, Friedmann PS, Matthews JN. Sex differences in susceptibility to development of contact hypersensitivity to dinitrochlorobenzene (DNCB). *Br J Dermatol* 1989; **120**:371–4.
25 Frain-Bell W, Johnson BE. Contact allergic sensitivity to plants and the photosensitivity dermatitis and actinic reticuloid syndrome. *Br J Dermatol* 1979; **101**:503–12.
26 Menage H, Ross JS, Norris PG *et al.* Contact and photocontact sensitization in chronic actinic dermatitis: sesquiterpene lactone mix is an important allergen. *Br J Dermatol* 1995; **132**:543–7.
27 Beattie PE, Traynor NJ, Woods JA *et al.* Can a positive photopatch test be elicited by subclinical irritancy or allergy plus suberythemal UV exposure? *Contact Dermatitis* 2004; **51**:235–40.

Appendix

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Supporting information

Additional supporting information is available in the online version of this article.

Appendix S1 Study proforma.

Appendix S2 Frequency of PACD at each recruiting centre.

Appendix S3 PACD reactions with COADEX assignations.

Appendix S4 Rates of PACD to the agents ketoprofen, etofenamate, octocrylene and benzophenone-3 in each country.

Appendix S5 COADEX assignations in the 15 subjects who had concomitant PACD reactions to benzophenone-3, octocrylene and ketoprofen.

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Report Title: **Skin Adverse Reactions with Topical Gels 2000-2010**

Prepared for: **OIA Request – TeArai BioFarma**

Prepared by: **New Zealand Pharmacovigilance Centre**
28 January 2015

Period Covered: This search covers all spontaneous reports received by the Centre for Adverse Reactions Monitoring [CARM] from 01 January 2000 to 31 December 2010

Request Details: Number of adverse skin reactions to diclofenac containing gels
Number of **serious** adverse skin reactions to diclofenac containing gels

Number of adverse skin reactions to ketoprofen containing gels
Number of **serious** adverse skin reactions to ketoprofen containing gels

Summary: Products meeting the criteria :

diclofenac containing gels	Voltaren Emulgel
ketoprofen containing gels	Oruvail Gel

Product	Total Reports 2000-2010	Skin Reaction	Serious Skin reaction
Voltaren Emulgel	26	6	0
Oruvail	1	1	0

Note: Seriousness is assessed for each report based on the 'result of the adverse event(s)'; the individual events are not separately assessed for seriousness. The international classification system assigns the following categories irrespective of whether there is a causal link between the event(s) and the product:

- Not serious
- Congenital abnormality
- Died
- Hospitalisation or prolonged hospitalisation
- Life Threatening
- Intervention required to prevent permanent harm
- Persisting disability at time of reporting

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CAVEAT DOCUMENT

Accompanying statement to data released from the

NEW ZEALAND CENTRE FOR ADVERSE REACTIONS MONITORING

The Centre for Adverse Reactions Monitoring (CARM) has only limited details about each suspected adverse reaction contained in its Database. It is important that the limitations and qualifications which apply to the information and its use are understood.

The data made available represent the collection of spontaneous reports in the CARM database associated with therapeutic products/vaccines granted regulatory approval for use in New Zealand.

Reports have been submitted to the Centre since April 1965 and in many instances describe no more than suspicions which have arisen from observation of an unexpected or unwanted event. This level of reporting is due to CARM encouraging reporters to report events they suspect may be associated with a pharmaceutical product/vaccine irrespective of whether or not they believe it was the cause. CARM accepts all reports and proof of causality is not required when submitting a report to CARM. Coincidental events that may be unrelated to pharmaceutical product/vaccine exposure may be reported. This is particularly possible when the product has widespread use, or is used in targeted strategies such as vaccination campaigns.

In most instances it cannot be proven that a pharmaceutical product or ingredient is the cause of an event in the Database. Reports vary in quality, completeness and detail and may include detail that is incorrect. Consequently, a report in the CARM database of an event does not confirm that the pharmaceutical product/vaccine caused the event.

The volume of reports for a particular product may be influenced by the extent of use of the product, publicity, nature of reactions and other factors which vary over time and from product to product. It is generally accepted internationally that systems such as CARM are subject to underreporting which may result in scant reports for events perceived by the reporter to be minor or well recognised, whilst more serious or unexpected events are possibly more likely to be reported, even if they are coincidental. Moreover, no information is provided on the number of patients exposed to the product.

The data contained in these tables are further subject to ongoing internal quality controls, review and updating and therefore may be subject to change, particularly if follow-up information is received.

For the above reasons interpretations of adverse reaction data, and particularly those based on comparisons between pharmaceutical products, may be misleading. Any use of this information must take into account at least the above. Although this information is now released, it is strongly recommended that prior to any use of such information, CARM is contacted for interpretation.

Any publication, in whole or in part, of the obtained information must have published with it a statement:

(i) of the source of the information

(ii) that the information is not homogenous at least with respect to origin or likelihood that the pharmaceutical product/vaccine caused the adverse reaction

(iii) that the information does not represent the opinion of the NZPhvC or CARM.

Director
New Zealand Pharmacovigilance Centre

Annex D

Reference:

http://sunsmart.org.nz

[redacted]

[redacted]

1st April 2015

The Secretary
Medicines Classification Committee
Medsafe
PO Box 5013
Wellington 6145
Dear Sir/Madam,

Re: Application for Reclassification – Response
Agenda Item 5.5 for the 53rd Medicines Classification Committee Meeting 5th May 2015
Subject: Paracetamol in combination with Phenylephrine

[redacted] would like to thank the Medicines Classification Committee (MCC) for the opportunity to comment on the proposed rescheduling / reclassification application requests for Paracetamol and Phenylephrine (PE) combination products which result in products that are currently either in pharmacy only or general sale being up-scheduled to restricted medicine (pharmacist supervising the sale).

[redacted] is a member of the New Zealand Self Medication Industry Association and their comments and recommendations with regards to the proposed rescheduling of paracetamol and phenylephrine combination products are fully endorsed by [redacted].

Historical Background

AFT Pharmaceuticals submitted an Application to amend the current scheduling /classification of paracetamol and phenylephrine combination products.

MCC included in the agenda of the 52nd meeting item 6.3 P**aracetamol in combination with phenylephrine** (Maxiclear Sinus and Pain Relief and Maxiclear Cold and Flu Relief, AFT Pharmaceuticals):

- Any number of solid dose units containing paracetamol 500 mg in combination with more than 2.5 mg phenylephrine per dose unit from general sale or pharmacy only medicine to restricted medicine
- More than 20 solid dose units containing paracetamol 500 mg in combination with 2.5 mg phenylephrine or less per dose unit to remain a pharmacy only medicine
- 20 or less solid dose units containing paracetamol 500 mg in combination with 2.5 mg phenylephrine or less per dose unit to remain a general sale
- Any number of sachets of powder containing 1000 mg paracetamol in combination with more than 5 mg phenylephrine per sachet from general sale or pharmacy only to restricted medicine

[redacted]

[redacted]

- More than 10 sachets of powder containing 1000 mg paracetamol in combination with 5 mg phenylephrine or less per sachet to remain pharmacy only
- 10 or fewer sachets of powder containing 1000 mg paracetamol in combination with 5 mg of phenylephrine or less per sachet to remain in general sale.

[redacted] submitted a response to the agenda for the 52nd MCC meeting held on the 21 October 2014 with reference to the item 6.3 Paracetamol in combination with Phenylephrine. [redacted] position was not supportive of the reclassification and recommended that the current classification remains appropriate.

The recommendations from the MCC on the 52nd meeting are as follows:
'That paracetamol in combination with phenylephrine should not be reclassified as proposed in the submission.
That the submission should be referred to Medsafe's Pharmacovigilance Team so that any adverse reactions from taking paracetamol in combination with phenylephrine could be actively monitored'.

Following publication of the minutes, AFT Pharmaceuticals informed Medsafe that the interaction between paracetamol and phenylephrine as a potential safety issue had been suggested by three additional studies as well as the single study published by the date of the last meeting.
The Committee will revisit their recommendation made at the 52nd meeting in light of these three studies.

[redacted]'s Position

[redacted] maintains the previous position of not supporting any of the amendments proposed in the application for reclassification of paracetamol and phenylephrine combination products.

The following points were considered in support of the above position:

- Further to the review of the 4 studies published in the EUR J Phamacol [1], [redacted] maintains the position to oppose the proposal for reclassification.

    - The three additional bioavailability studies referenced by AFT Pharmaceuticals (AFT) do not add any clinical evidence on the effects on blood pressure (BP) or heart rate (HR).
      There is no evidence to suggest that AFT provided any supportive clinical safety and efficacy studies. Rather it appears AFT relied on the increase in AUC or Cmax to derive a blood pressure range for phenylephrine 10mg and paracetamol 1000mg.

    - The studies were conducted in very restricted conditions:
        - in a small group
        - of healthy individuals
        - all males
        - from only one region
        - the participants had been fasting for 12 hours (not the usual condition, when talking the medicine)

[1]Atkinson HC, Stanescu I, Salem II, EUR J Phamacol (2015) 71 151:158

[redacted]

[redacted]

The minutes of the 52nd MCC meeting states that '*the studies would need to be repeated with a larger, more varied cohort of research participants in different regions to see if the results would be replicated. The research participants had been fasting for 12 hours whereas typically patients taking the medicine would not'.*

These comments were not addressed in any of the published studies. The studies will need to be repeated addressing all points above including the clinically significance of the interaction. Currently the proposed amendment for reclassification is only based in a potential clinical interaction. There are no other studies with similar findings conducted elsewhere.

- There are no significant number of adverse events reports of BP, HR or other cardiovascular problems associated with phenylephrine combination products in the Australian or New Zealand adverse databases in the period between Jan 2000 & Dec 2014, especially considering the widespread use of phenylephrine in cough & cold medications.

- In Australia, the paracetamol and phenylephrine combination products carry labelling warnings as per the TGA Medicines Advisory Statements Specification (MASS) 2014, advising people with heart conditions and hypertension to consult their doctor or pharmacist before use.
  'See your doctor or pharmacist before taking [this product/insert name of product] if you have high blood pressure or heart problems'.
  In addition to comply with [redacted] core data sheet, all [redacted] products containing phenylephrine, marketed in Australia or New Zealand, in compliance with corporate requirement include the following warning statement:
  "*Ask your doctor before use if you are presently taking or have recently taken blood pressure medicine or sympathomimetics*"

- [redacted] conducted a literature search for all time until 31 July 2014 for drug interaction between phenylephrine and paracetamol. No relevant articles have been retrieved.

- The Medicine Classification Committee also noted a large number of products would be affected by a reclassification in New Zealand. NSZMI suggested in the previous submission that there are in excess of 100 products in various pack sizes that contains paracetamol combined with phenylephrine.

- The TGA delegate's final decision (reasons Medicines scheduling March 2015), with reference to the proposal for reclassification of products containing paracetamol in combination with phenylephrine was that *'that the current scheduling of paracetamol in conjunction with phenylephrine remains appropriate'.*

Conclusion:

For all reasons stated above [redacted] *recommendation is 'that the current scheduling of paracetamol in conjunction with phenylephrine remains appropriate'.*

[redacted]

[redacted]

Request for Confidentiality

I would be grateful if you would have my name and contact details as well as sponsor's name removed from any public version of the submission. I also would like my name to be removed from all documents prior to publication and not be included within the list of submissions on the Medsafe website.

Yours sincerely,

[redacted]

[redacted]
Regulatory Manager

[redacted]

29 March 2015

Andrea Kerridge (Secretary)
Medicines Classification Committee
PO Box 5013
WELLINGTON

Application for Further Reclassification

Agenda Item for the 53rd Medicines Classification Committee Meeting
May 2015

SUBJECT: Paracetamol in combination with Phenylephrine (AFT Pharmaceuticals)

Dear Secretary

The New Zealand Self Medication Industry (NZSMI) is the representative trade organisation for the major *"over the counter"* (OTC) medicine sponsor companies within New Zealand.

We appreciate the opportunity to make comment on the agenda item and hope our comments are taken in a constructive manner to assist in the committee's decision.

Yours faithfully

Tim Roper
Executive Director
New Zealand Self-Medication Industry

EXECUTIVE SUMMARY

- This further request from AFT Pharmaceuticals for the MCC to reconsider their initial decision with regard to Paracetamol and Phenylephrine in combination- in NZSMI's view is flawed as AFT has not addressed the major comments raised by the Committee in October 2014, i.e:

  > *"(1) That a larger more varied cohort of research participants in different regions to see if the results would be replicated, has taken place."*

- Secondly, the further evidence presented via the three extra studies does not alter the point raised by the Committee, *"that the amount of data and information presented with the submission was hypothesis generating at this stage"*.

- Thirdly, the Committee considered *"that there was still a question over clinical relevance of this pharmacokinetic interaction given the lack of reported adverse events and volume of use of phenylephrine over many years"*. We do not believe that this further evidence addresses this point raised by the Committee.

- *"The Committee also noted a large number of products would be affected by a reclassification"*. NZSMI further states that this remains a major issue and the further evidence produced by AFT does not warrant such reclassification as proposed.

- NZSMI, in its investigation, has found no evidence of adverse reactions from taking paracetamol in combination with phenylephrine which was an indicator given from the MCC by directing Medsafe's Pharmacovigilance team to monitor adverse reactions. We do not believe that the Pharmacovigilance team will have found any different results than those obtained by NZSMI.

SUMMARY

With regard to our first point in the Executive Summary we wish to clarify further:

In the agenda for the upcoming meeting:

"AFT Pharmaceuticals informed Medsafe that the interaction between paracetamol and phenylephrine, as a potential safety issue, has now been suggested by three additional studies, as well as the single study published at the date of the last meeting"

NZSMI believes this statement to be misleading as it suggests that a further large body of work has been undertaken. This is not the case. The "single study" published for the last meeting was a Letter to the Editor, referring to three studies that are actually included within the new paper. If the "letter" is read it states that *"Three randomised, open-label, crossover studies in healthy volunteers were undertaken as part of the development of a new fixed dose combination containing acetaminophen, ibuprofen and phenylephrine"*

These same studies are referred to in the "new" paper presented, with the graph of the pharmacokinetic interaction in the first letter to the editor being identical to that shown in the new study (page 155) as "Study 1" treatment A versus treatment B. The new report also states that it has pooled the results of previous pharmacokinetic studies (three of which have been referred to in the letter).

NZSMI therefore questions whether or not this represents "new data"-we would take the view that it is more complete reporting of existing data.

A further separate argument for no change to the current classification relates to the decision made by the ACMS after considering an application made at their November 2014 meeting. The reasons for no change in Australia are given in the *Delegates reasons for decisions:*

https://www.tga.gov.au/book/part-final-decisions-matters-referred-expert-advisory-committee-11-14#pheny

Amongst the reasons for not recommending a change to the schedules, the delegate states *"that no evidence was provided that the increased bioavailability of PE that was observed had any clinical meaningful effects on blood pressure or heart rate".*

NZSMI prepared a response to Agenda item 6.3 for the 52nd Medicines Classification Committee meeting on 21 October 2014 on this topic. We again restate the points made in that submission as:

- Paracetamol and phenylephrine has had extensive use as a pharmacy only and general sales medicine with millions of units sold annually with no significant adverse events relating to cardiovascular disease or hypertension. The proposal for restricting supply to restricted medicine is based on a theoretical safety concern which has not been reflected in company or public adverse event databases.

- The absence of safety signals indicates that the combination of paracetamol and phenylephrine represents no safety concern. Any theoretical or predicted issue should be addressed in extensive appropriately designed and robust wide ranging clinical studies (*we note that this was a suggestion made by the MCC at their meeting in October 2014, which in our view, has not been addressed by AFT Pharmaceuticals*).

  Paracetamol and phenylephrine combination products are used for short term symptomatic cold and flu symptom relief, therefore the effects on blood pressure will be short lived and of limited clinical significance for the vast majority of people who use the product.

- Up-scheduling this combination to restricted medicine will not be in the best interest of public health and will increase the workload burden on pharmacists given the sound safety profile of this combination and the years of extensive use of these medicines with no significant adverse events data reported to date.

- The proposed changes would have a significant impact on sponsors and their products and would cause confusion to consumers in terms of the way in which the medicines can be purchased without any sound safety concerns to justify the move.

- NZSMI is of the opinion that the three additional studies provided by AFT do not add any further significant evidence to the one study (published) that was provided for the October 2014 meeting. Fundamentally the issues that were raised by the MCC for AFT to address prior to a review of the decision appear to have been largely ignored.

Rather than re-litigate all the points that were raised in our initial submission on 12 September 2014, we have added this paper as an **Appendix** to the current submission.

NZSMI is willing to be involved in further discussions with the MCC if that is felt to be of value.

APPENDIX

EXECUTIVE SUMMARY

- Paracetamol and phenylephrine has had extensive use as pharmacy only and general sales medicine with millions of units sold annually with no significant adverse events relating to cardiovascular disease or hypertension. The proposal for restricting supply to restricted medicine is based on a theoretical safety concern which has not been reflected in company or public adverse event databases.

- The absence of safety signals indicates that the combination of paracetamol and phenylephrine represents no safety concern. Any theoretical or predicted issue should be addressed in extensive, appropriately designed and robust wide ranging clinical studies. Paracetamol and phenylephrine combination products are used for short term symptomatic cold and flu symptoms relief, therefore the effects on blood pressure will be short-lived and of limited clinical significance for the vast majority of people who use the product.

- Up-scheduling this combination to restricted medicine will not be in the best interest of public health and will increase the workload burden on pharmacists given the sound safety profile of this combination and the years of extensive use of these medicines with no significant adverse events data reported to date.

- The proposed changes would have a significant impact on sponsors and their products and would cause confusion to consumers in terms of the way in which the medicines can be purchased without any sound safety concerns to justify the move.

APPLICATION FOR RECLASSIFICATION FOR PARACETAMOL AND PHENYLEPHRINE COMBINATION

- Any number of solid dose units containing paracetamol 500 mg in combination with more than 2.5 mg phenylephrine per dose unit from general sale or pharmacy only medicine to restricted medicine

- More than 20 solid dose units containing paracetamol 500 mg in combination with 2.5 mg phenylephrine or less per dose unit to remain a pharmacy only medicine

- 20 or less solid dose units containing paracetamol 500 mg in combination with 2.5 mg phenylephrine or less per dose unit to remain a general sale.

- Any number of sachets of powder containing 1000 mg paracetamol in combination with more than 5 mg phenylephrine per sachet from general sale or pharmacy only to restricted medicine.

- More than 10 sachets of powder containing 1000 mg paracetamol in combination with 5 mg phenylephrine or less per sachet to remain pharmacy only

- 10 or fewer sachets of powder containing 1000 mg paracetamol in combination with 5 mg of phenylephrine or less per sachet to remain in general sale

BACKGROUND

The proposed rescheduling application requests an upward scheduling for existing, currently marketed paracetamol and phenylephrine combination products, which would result in products that are currently either in pharmacy only or GSL being up-scheduled to restricted medicine (pharmacist supervising the sale).

NZSMI understands that an application has also been submitted by AFT to the ACMS for their forthcoming meeting in Australia. NZSMI contends that there are hundreds of combination paracetamol plus phenylephrine products in a number of pack sizes currently registered in New Zealand that would be affected by such a rescheduling. NZSMI does not agree that the existing pharmacy only and GSL paracetamol and phenylephrine combination products meet the criteria for a restricted medicine classification and strongly opposes the above rescheduling proposal.

NZSMI is of the view that this application for rescheduling is based primarily on one piece of evidence.

- A letter to the editor of the New England Journal of Medicine (NEJM)[1] which describes a pharmacokinetic study that was undertaken on a combination paracetamol /ibuprofen/ phenylephrine product in development, which showed an incidental finding of mean plasma levels of phenylephrine being higher when phenylephrine is co-administered with paracetamol.

[1] Atkinson HC, Stanescu I. Increased phenylephrine plasma levels with administration of Acetaminophen. N. Eng J Med 2014; 370(12):1171-2

The authors proceed to describe a purported pharmacological interaction between paracetamol and phenylephrine, stating that paracetamol increases the bioavailability of phenylephrine, resulting in increased plasma levels of phenylephrine.

Assuming that the basis of the rescheduling application relates to the single item of evidence described above, the author's stated rationale for restricting supply of the paracetamol 500mg plus phenylephrine 5mg to pharmacist only is based on theoretical safety concerns regarding the use of currently registered pharmacy only and GSL products by consumers.

NZSMI comment on the basis for the rescheduling application

The applicant states that "*Paracetamol and phenylephrine combinations have been available in New Zealand and* ***the rest of the world since 2006*****…..**" The fact is this combination has been extensively used within the community and in the UK since as early as 1997. Therefore there has been extensive global market experience within the OTC environment.

Despite this extensive use within the community there is no evidence of any documented safety issues that could justify the up-scheduling of these medicines to restricted medicine. These products have had many years of use and have a favourable safety profile.

These products are used for symptomatic relief of cold and flu, for short treatment duration. Products are labelled with appropriate safety warning statements as dictated by Medsafe, the Regulator, which advise the patient whether or not to seek the advice of a doctor or other health professional before taking the medicine; specifically if the patient has high blood pressure or heart problems or is taking other medication that could interact with the product.

Consumers who are aware that they have heart conditions or hypertension are clearly advised to consult their doctor or pharmacist. We note in the application from AFT that the authors raise safety concerns relating to the possible scenario of use of the existing combination paracetamol and phenylephrine combination products by people with undiagnosed hypertension.

In this submission the applicant contends that moving these products to restricted medicine will reduce the risk to consumers who may have undiagnosed hypertension. NZSMI contends this is purely an assumption based on no firm evidence. Pharmacists will not be in a position to diagnose individuals who have cardiovascular conditions or hypertension in any case, and their questioning of consumers will be informed by warning statements that are present on the label and in the pharmacy texts, such as the New Zealand formulary or MIMS. Pre-diagnosis of cardiovascular disease or hypertension is not something carried out by pharmacists prior to recommending particular products.

Although a relationship between sympathomimetic drugs (such as phenylephrine) and vasopressor effects has been documented and has a pharmacological basis, a base literature search (Pub Med) has not revealed any studies documenting any specific dose response relationship between phenylephrine/phenylephrine combined with paracetamol and blood pressure. Considering the product usage is for short term symptomatic relief, any effect on blood pressure will be short lived and of a limited **clinical significance** for the vast majority of people who use the product.

Impact of possible rescheduling

There are well in excess of 100 products in various pack sizes that contain paracetamol combined with phenylephrine. To NZSMI's knowledge all of the products currently on the New Zealand market are either oral tablets/caplets/capsules containing paracetamol 500mg and phenylephrine 5mg or granules/powders containing paracetamol 1,000mg plus phenylephrine 10mg. All of these products would be affected by this rescheduling if it were to be implemented.

There would be a significant business impact for existing sponsors should such a change take place, as well as consumer confusion for the many consumers who are familiar with the products existing availability in pharmacy as a pharmacy only medicine and as GSL within the grocery sector.

Pharmacists will also be significantly affected by the volume of queries and requests from consumers for these commonly used products; it is likely that this will have an unwanted effect on the day to day practice of busy pharmacists due to the high volume of these products supplied under well-known brand names that would switch to pharmacist only.

NZSMI recommendations

NZSMI does not support the proposal to amend the scheduling of paracetamol plus phenylephrine combination products and believes that the current scheduling remains appropriate.

There is no documented safety issue with the existing products and the way that they are scheduled. NZSMI believes that up-scheduling should only take place when a public health risk is demonstrated and the scheduling proposal does not appear to meet this criterion.

The banning of pseudoephedrine containing products in New Zealand occurred as a consequence of a public campaign that indicated that methamphetamine production from pseudoephedrine was causing a rise in crime within the country. It could be argued that the public benefit gain was achieved by removing these products from sale. Similarly codeine containing analgesics have been up-scheduled where there has been firm evidence to suggest that the public would benefit from such a move. The rationale for this rescheduling application appears to fall far short in comparison.

The NEJM letter showing an observed increase in plasma levels of phenylephrine when co-administered with paracetamol is interesting but does not justify the significant impact on the business of sponsors and pharmacists. NZSMI made a media statement on 21 March 2014 similarly commenting on the fact that the new information was of interest but limited in the sense that more work was required before changes to reclassification would be merited. Indeed Medsafe at that time commented that it had seen the data but had no concerns for patient harm given the 40 year history of the drug where millions of doses had been administered.

In the application for reclassification AFT suggest that there have been 28 adverse events to phenylephrine in 11 separate reports to Medsafe from 1 January 2000 to 1 July 2014. No deaths have been reported. This represents 2 adverse events per year. It is difficult to put a number on how many patients have been treated with products containing paracetamol and phenylephrine in combination in a similar period, but it would run into millions of patients and millions of doses. When that is put into context it is clear that the clinical risk to patients taking these products for short term durations to alleviate the symptoms of sinus and the common cold and flu, should not give rise to any serious safety concerns.

Medicines Classification Committee

Meeting date	5 May 2015	Agenda item	6.1
Title	**Overview of Nitrofurantoin Safety**		
Submitted by	Medsafe Pharmacovigilance Team	Paper type	For information
Proposal for reclassification to restricted medicine	Prescription only except in medicines for oral use containing 50 mg per dose unit when sold in a pack of 20 solid dosage units to a woman aged 16-65 years for the treatment of an uncomplicated lower urinary tract infection by a registered pharmacist who has successfully completed the New Zealand College of Pharmacists' training course in the treatment of urinary tract infections, where supply adheres to the screening tools approved by the Pharmaceutical Society of New Zealand		
Reason for submission	The purpose of this document is to provide the committee with information about safety concerns associated with nitrofurantoin use.		
Associated *Prescriber Update* articles	June 2012	Nitrofurantoin – Do the Benefits Outweigh the Risks Long-Term?	
	June 2006	Nitrofurantoin – Monitor Lung Function in Long-Term Use	
	May 2002	Pulmonary Reactions with Nitrofurantoin	
New Zealand exposure to nitrofurantoin	January 2014 – December 2014	Approximately 6,000 – 7,000 prescriptions dispensed per month	

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1.0 PURPOSE

A submission for reclassification of nitrofurantoin has been made by Green Cross Health Limited. The proposed reclassification is from prescription medicine to restricted medicine in tablets containing 50 mg nitrofurantoin or less, when dispensed in packs of 20 tablets, for the treatment of uncomplicated cystitis in women aged 16-65 years.

The purpose of this document is to provide the committee with information about the safety of nitrofurantoin. Given that the proposed use of nitrofurantoin is for 5 days of treatment, this review will focus on acute reactions.

2.0 BACKGROUND

Nitrofurantoin is currently classified as a prescription only medicine. It was first approved for use in New Zealand in 1969 and is indicated for the prophylaxis and treatment of infections of the genito-urinary tract due to susceptible bacteria.

Nitrofurantoin is readily absorbed following oral administration. The presence of food can further increase the availability as well as enhancing tolerability. The exact mode of action of nitrofurantoin is not completely understood, but nitrofurantoin is known to inhibit a number of bacterial enzymes that inhibit bacterial carbohydrate metabolism at different points in the Krebs cycle[1].

Approximately 75% of the absorbed dose is rapidly metabolised by the liver (glutathione s-reductase), but 25% is excreted in the urine unchanged. Tubular reabsorption of nitrofurantoin is pH dependent, and reabsorption is promoted by acid urine (pH ≤ 5.5). Conversely, tubular reabsorption is decreased by alkaline urine, which results in the concentration of nitrofurantoin in the bladder[1]. Nitrofurantoin efficacy in lower urinary tract infections is dependent upon it being concentrated in the bladder. Due to the metabolism and excretion properties, blood plasma levels of nitrofurantoin in healthy subjects are low.

In subjects with reduced renal function there may be more systemic accumulation and less urinary accumulation, which increases the risk of adverse effects and reduces the efficacy. For these reasons nitrofurantoin is contraindicated in patients with a creatinine clearance less than 60 mL/min.

Nitrofurantoin is also contraindicated in pregnant women during labour and delivery, or when the onset of labour is imminent, because of the possibility of haemolytic anaemia; and in patients with known hypersensitivity to nitrofurantoin.

The usual dose of nitrofurantoin for acute, uncomplicated urinary tract infections is 50-100 mg four times a day for 7 days. The usual prophylactic dose is 50-100mg at bedtime. Duration of long-term prophylaxis is up to 6 months and should only be continued beyond this period when the benefits of therapy clearly outweigh the potential risks.

2.1 Usage data

During 2014, a total of 80,385 prescriptions for nitrofurantoin were dispensed in the community in New Zealand (Table 1). The number of dispensings was consistent across all months. The mean daily dose or whether use was for acute infection or long-term prophylaxis cannot be determined from these figures.

[1]Cunha A. (1989). Nitrofurantoin: An Update. *Obstet Gynecol Surv* 44(5): 399-406

Table 1: Prescriptions dispensed per month in 2014

Number of Prescriptions	Month 2014
6,624	January
5,976	February
6,646	March
6,515	April
7,047	May
6,487	June
7,153	July
6,695	August
6,898	September
6,999	October
6,353	November
6,992	December

2.2 Spontaneous reports in New Zealand

The Centre for Adverse Reactions Monitoring (CARM) has received 319 adverse reaction reports, containing 604 reactions, where nitrofurantoin was considered as a suspect medicine regardless of the level of causality (since database inception). Of these reports, 42% (n=134) had an onset time of less than one week, 17% (n=53) less than one month and 33% (n=106) more than one month. The duration to onset was unknown in 8% of reports (n=26).

Table 2 shows the onset time of the reaction by age group. This table shows that although the incidence of adverse reactions increases with increasing age, these still occur amongst all age groups.

It is not known if nitrofurantoin was still being taken when the reactions occurred or whether nitrofurantoin was being taken for acute infection or long-term prophylaxis. For example, the patient may have taken a 5 day course, but the reaction started one month later or the reaction occurred within the first week of long-term, lower daily dose, prophylactic therapy.

Table 2: Reaction onset time by age group

Age	< 1 week	< 1 month	> 1 month	Unknown	Total
< 20 years	4	1	0	0	**5**
20 – 29 years	10	4	1	0	**15**

30 – 39 years	14	6	4	0	**24**
40 – 49 years	13	4	7	3	**27**
50 – 59 years	33	6	14	3	**56**
60 – 69 years	23	13	23	6	**65**
> 70 years	37	18	57	14	**126**
Unknown	0	1	0	0	**1**
Total	**134**	**53**	**106**	**26**	**319**

Reactions were also grouped according to the system organ class (SOC). Table 3 shows the distribution of reactions according to SOC by onset time, where each SOC was counted only once per report. For example, if there were two reactions from one report from the same SOC then this was counted only once and if there was a report with reactions from more than one SOC, the report was counted one time for each SOC (n=511).

Table 3: Reaction type (system organ class)* by onset time

System Organ Class	< 1 week	< 1 month	> 1 month	Unknown	Total
Alimentary	37	9	4	2	52
Cardiovascular	15	4	1	3	23
Collagen Disorders	0	0	1	0	1
Endocrine/Metabolic	1	1	2	0	4
Haematological	3	4	1	1	9
Liver	7	5	21	4	37
Musculoskeletal	10	4	0	2	16
Nervous System	19	9	25	2	55
Others	33	13	7	7	60
Procedure Related	0	0	2	0	2
Psychiatric Changes	10	3	1	3	17
Resistance Mechanism Disorders	1	0	0	0	1
Respiratory	33	23	61	14	131
Skin and Appendages	65	27	6	4	92

Special Senses	4	0	0	1	5
Urinary	2	1	3	0	6
Total	240	93	135	43	511

*According to WHO-ART terminology

This table shows that the distribution of reaction onset time was varied and depended on the type of reaction grouping. For example, there were 92 reports with reactions in the skin and appendages SOC; however the majority (n=65) occurred within the first week.

The time to reaction onset distribution was different within the respiratory SOC. There was a more even split between reactions that occurred acutely compared with those that occurred with ongoing nitrofurantoin use. This reflects the difference in pulmonary reactions (both acute hypersensitivity and chronic infiltration) that occur with nitrofurantoin use.

Individually, the reactions most frequently reported included rash (n=47), dyspnoea (n=32), fever (n=29), vomiting (n=26), pulmonary fibrosis (n=26), nausea (n=20), coughing (n=20), pneumonia interstitial (n=16), neuropathy (n=15), interstitial lung disease (n=15), headache (n=14), rigors (n=11) and peripheral neuritis (n=10).

The respiratory, skin and appendages, nervous system and alimentary SOC groups were the SOC groups with the most reactions and the most commonly reported individual reactions were representative of this.

3.0 DATA SHEET INFORMATION

The currently available nitrofurantoin data sheet provides information about potential adverse reactions.

Contraindications:

Anuria, oliguria or significant impairment of renal function (creatinine clearance under 60 mL per minute or clinically significant elevated serum creatinine) are contraindications. Treatment of this type of patient carries an increased risk of toxicity because of impaired excretion.

Due to the possibility of haemolytic anaemia due to immature erythrocyte enzyme systems (glutathione instability), nitrofurantoin is contraindicated in pregnant women during labour and delivery, or when the onset of labour is imminent. Nitrofurantoin is also contraindicated in neonates less than one month of age due to the same reason and in patients with known hypersensitivity to nitrofurantoin.

Warnings:

Acute, subacute or chronic pulmonary reactions. Chronic pulmonary reactions (diffuse interstitial pneumonitis or pulmonary fibrosis, or both) can develop insidiously and are generally in patients receiving therapy for six months or longer. If pulmonary reactions occur (whether acute or chronic), nitrofurantoin should be discontinued and appropriate measures taken.

Fever, chills, cough, chest pain, dyspnoea, pulmonary infiltration with consolidation or pleural effusion on x-ray and eosinophilia are symptoms of acute pulmonary reactions. Acute reactions usually occur within the first week of treatment and are reversible with cessation of therapy. In subacute pulmonary reactions, fever and eosinophilia occur less often than in the acute form. Upon cessation of therapy, recovery may require several months.

Hepatic reactions (including hepatitis, cholestatic jaundice, chronic active hepatitis and hepatic necrosis) occur rarely. Chronic active hepatitis can develop insidiously and patients should be monitored periodically for changes in liver function.

Peripheral neuropathy (including optic neuritis) has occurred, which may become severe or irreversible. Conditions such as renal impairment, anaemia, diabetes mellitus, electrolyte imbalance, vitamin B deficiency and debilitating disease may enhance the occurrence of peripheral neuropathy.

Haemolytic anaemia of the primaquine-sensitivity type has been induced by nitrofurantoin. Haemolysis appears to be linked to a glucose-6-phosphate dehydrogenase deficiency in the red blood cells of the affected patients.

Interactions:

Magnesium trisilicate (eg, Quick-eze, some Gaviscon products) may impair both the rate and extent of absorption.

Uricosuric drugs (such as probenecid) can inhibit renal tubular secretion of nitrofurantoin, which may increase serum nitrofurantoin levels and decrease urinary levels.

Adverse effects:

Nausea, headache and flatulence most commonly reported.

Allergic and dermatologic reactions have also been reported (including pruritus, urticaria, lupus-like syndrome associated with pulmonary reactions, angioedema, anaphylaxis, exfoliative dermatitis and erythema multiforme), as well as those already discussed in the warnings section (neurologic, respiratory and hepatic reactions).

4.0 PUBLISHED LITERATURE

Medsafe performed a review of the literature, however as nitrofurantoin has been available since 1953 (New Zealand in 1969), the available literature is often outdated or does not adequately address all of the acute adverse effects of nitrofurantoin. Much of the literature is in relation to pulmonary toxicity associated with prolonged nitrofurantoin treatment for prophylaxis of recurrent urinary tract infections.

The main concerns with acute nitrofurantoin use include pulmonary reactions, skin reactions, blood disorders and hepatotoxicity. Pulmonary reactions associated with nitrofurantoin have been known since the 1960's[2,3]. Acute pulmonary reactions typically have hypersensitivity-type features and mainly affect women aged 40-50 years[4].

4.1 Holmberg et al. (1980)[5]

An analysis of 921 adverse reaction reports to nitrofurantoin made to the Swedish Adverse Drug Reaction Committee (from 1966 until 1976) was conducted to determine the types of adverse reactions experienced. The types of adverse reactions could be grouped into six categories and are show in Table 4 – acute pulmonary reactions, chronic pulmonary reactions (interstitial pneumonitis),

[2]Murray MJ and Kronenberg R. (1965). Pulmonary Reactions Simulating Cardiac Pulmonary Edema Caused by Nitrofurantion. *N Engl J Med* 273: 1185-1187
[3]Anonymous. (1969). Lung disease caused by drugs. *Br Med J* 3(5673):729-730
[4]Tatley M. (2002). Pulmonary Reactions with Nitrofurantoin. *Prescriber Update* 23(2) 24-25 (www.medsafe.govt.nz/profs/PUarticles/nitrofurant.htm)
[5]Holmberg L, Boman G and Bottiger LE. (1980). Adverse Reactions to Nitrofurantoin: Analysis of 921 Reports. *Am J Med* 69(5): 733-738

allergic reactions (various cutaneous manifestations, anaphylactic reactions), liver damage, blood dyscrasias and neuropathy.

Table 4: Adverse reactions to nitrofurantoin, 1966-1976

		Total Patients		Hospitalized Patients		Fatal Cases	
		No.	%	No.	%	No.	%
Pulmonary reactions		447	48	337	75		
Acute pulmonary hypersensitivity	398					2	0.5
Chronic interstitial pneumonitis	49					4	8
Allergic reactions		384	42	243	63	—	—
Liver damage		50	6	38	76	1	2
Blood dyscrasias		20	2	20	100	4	20
Neuropathy		20	2	13	65	—	—
		921	100	651	71	11	1

Pulmonary reactions, particularly acute pulmonary hypersensitivity, comprised almost half of all adverse reaction reports, followed by allergic reactions. Women made up 86% of all patients; with the median age 62 years (mean age 59 years). There were also fatalities associated with nitrofurantoin use, including two with acute pulmonary hypersensitivity reactions.

The doses at which adverse reactions occurred were not noted in this study and it was also not known if patients were still taking nitrofurantoin at the onset of adverse reactions.

While more patients had more than one symptom, fever was the most common initial symptom that triggered the patient to seek medical advice, followed by dyspnoea, exanthema and dry unproductive cough (Table 5).

Table 5: Initial symptoms in nitrofurantoin reactions (one or more symptoms per patient)

Symptoms	No.	%
Fever (≧38°C)	646	70
Dyspnea	312	34
Exanthema	261	28
Dry cough	241	26
Fatigue	106	12
"Flu"	87	9
Cyanosis	36	4
Jaundice	29	3
Weight loss	22	2
Total	1,740*	

* Symptoms in 921 patients (1.9 per patient).

The duration of treatment with nitrofurantoin before symptom onset varied considerably. The majority, 697 patients, had received treatment for less than one month (Table 6). Short-term treatment predominated among those with acute pulmonary and allergic reactions, whereas chronic pulmonary reaction and those with liver damage were receiving long-term treatment.

Table 6: Duration of last continuous therapy before onset of symptoms, number of patients

Type of Reactions	Duration				
	<1 mo	1–12 mo	>12 mo	Unknown	Total
Pulmonary, acute	343 (86)*	10	5	40	398
Pulmonary, chronic	1	18	23 (47)	7	49
Allergic	311 (81)	13	—	60	384
Liver damage	23 (46)	6	12	9	50
Blood dyscrasias	10 (50)	3	1	6	20
Neuropathy	9 (45)	7	1	3	20
Totals	697 (76)	57 (6)	42 (5)	125 (14)	921 (100)

* The most common period of treatment in each type of reaction is indicated by a percentage figure (figures in parentheses).

Almost half of patients (409 patients) were taking medicines other than nitrofurantoin, but the Committee had not regarded the concurrent medication as related to the adverse reaction in 97% of these cases. In the remaining 3% of cases the adverse reaction was attributed to both nitrofurantoin and another medicine.

A total of 172 patients knew they had been given one or more courses of nitrofurantoin prior to the present episode and just more than half of these reported that they had had previous adverse reactions to nitrofurantoin. At the time of adverse reaction report submission, 58% of patients had made a complete recovery and 16% a partial recovery. It was noted that the reactions, in the lungs as well as in the skin, all carry the characteristics of an acute hypersensitivity reaction, with many patients sensitised by previous treatment.

Medsafe comment:

Although this study was conducted in Sweden and therefore may not be generalizable to the New Zealand population, it provides an analysis of potential adverse reactions associated with nitrofurantoin treatment.

Acute pulmonary reactions comprised almost half of all adverse reaction reports and onset was generally within one month of treatment initiation. Fever, dyspnoea and dry cough, symptoms all reported frequently in this study, are indicative of respiratory adverse effects. If the Committee does reclassify nitrofurantoin then there should be particular consideration of how fever management will be communicated to the patient as fever is both a sign of infection as well as an initial symptom of a pulmonary reaction, and how this will be differentiated.

The acute hypersensitivity reaction in many patients was due to sensitisation from previous treatment, therefore consideration with regards to the frequency of repeat nitrofurantoin treatment is required to potentially minimise this risk. It is recommended that those who have had an acute pulmonary reaction should not take nitrofurantoin again.

4.2 Koch-Weser et al. (1971)[6]

An analysis of 2,118 courses of antimicrobial therapy (sulfisoxazole, sulfamethoxazole or nitrofurantoin) in patients hospitalised at the Massachusetts General Hospital between April 1967 and July 1968 was conducted to determine adverse reactions. Patients were monitored for three days or until hospital discharge or death. Those that experienced adverse reactions were followed until the reaction had completely cleared.

[6]Koch-Weser J, et al. (1971). Adverse Reactions to Sulfisoxazole, Sulfamethoxazole and Nitrofurantoin. *Arch Int Med* 128: 399-404

Adverse reactions were considered as related to the treatment when they could not be attributed to the patient's underlying disease or to other therapy, and which cleared when therapy was ceased. Adverse reactions that required specific treatment, reduction or cessation of therapy with the offending medication were included.

Table 7: Reaction rates to individual medicines

	Total Utilizations	Total Reactions		Toxic Reactions		Allergic Reactions	
	No.	No.	Reaction Rate (%)	No.	Reaction Rate (%)	No.	Reaction Rate (%)
Sulfisoxazole	1,002	30	3.1	3	0.3	28	2.8
Sulfamethoxazole	359	12	3.3	1	0.3	11	3.0
Nitrofurantoin	757	70	9.2	39	5.1	31	4.1

Table 8: Types of reactions

	Sulfisoxazole and Sulfamethoxazole		Nitrofurantoin	
Dermatologic reactions	29		15	
Macular eruption		7		3
Maculopapular eruption		6		4
Urticarial eruption		5		3
Angioneurotic edema		2		1
Erythema multiforme		2		1
Pruritus only		2		0
Other eruptions (Purpuric, petechial, vesicular erythema nodosum, exfoliative dermatitis)		5		3
Gastrointestinal reactions	8		75	
Anorexia, nausea		3		38
Vomiting		3		28
Abdominal pain		1		4
Gastrointestinal bleeding		1		2
Diarrhea		0		3
Hematologic reactions	20		13	
Eosinophilia		16		10
Hemolytic anemia		1		1
Megaloblastic anemia		0		1
Leukopenia		1		1
Thrombocytopenia		1		0
Hypoprothrombinemia		1		0
Drug Fever	16		15	
Serum sickness	1		2	
Vasculitis	1		1	
Cholestatic jaundice	1		0	
Pulmonary infiltration	0		2	
Polyserositis	0		1	
Polyneuropathy	0		1	

The incidence of adverse reactions to nitrofurantoin was higher than to the sulfonamides (Table 7). Gastrointestinal reactions comprised the majority of all reactions and were far more common during nitrofurantoin therapy than with the sulfonamides (Table 8). However, the gastrointestinal reactions were considered to be mild in the majority of cases. The risk of an adverse reaction was positively associated with duration of exposure.

A total of 80% of the observed toxic reactions to nitrofurantoin occurred within the first six days of treatment and no further reactions occurred after the 16th day of treatment. Allergic reactions to nitrofurantoin were also highest during the first week, but continued to occur during the 3rd and 4th week of treatment.

Table 9 shows the age-specific adverse reaction rates. Age was not considered a factor in the rate of either toxic or allergic reactions for the two sulfonamides or nitrofurantoin, although the frequency was lowest in children.

Table 9: Age-specific reaction rates

Age	Total Utilizations	Toxic Reactions		Allergic Reactions	
	No.	No.	Reaction Rate (%)	No.	Reaction Rate (%)
	Sulfisoxazole and Sulfamethoxazole				
<15	120	0	0.0	1	0.8
15 to 44	284	1	0.4	10	3.5
45 to 64	379	1	0.3	14	3.7
65 to 74	292	1	0.3	8	2.7
>74	286	1	0.3	6	2.1
Total	1,361	4	0.3	39	2.9
	Nitrofurantoin				
<15	95	1	1.1	3	3.2
15 to 44	122	9	7.4	6	4.9
45 to 64	229	11	4.8	16	7.0
65 to 74	168	8	4.7	5	3.0
>74	143	10	7.0	1	0.7
Total	757	39	5.1	31	4.1

No new types of adverse reactions were detected in this study, likely due to the low numbers of patients included. The rate of untoward effects severe enough to require discontinuation of therapy was higher for nitrofurantoin than for the sulfonamides.

Medsafe comment:

This study shows that incidence of adverse reactions is not specifically age-related. Although in general the incidence of adverse reactions increases with increasing age, this study has shown that all age groups treated with nitrofurantoin are at risk of adverse reactions. This information, along with age-related information reported to CARM should be considered by the committee.

4.3 Cunha (1989)[1]

With regards to the safety profile of nitrofurantoin, the overall incidence of adverse reactions is very low. However, clinicians must still be aware of the potential adverse reactions, including pulmonary infiltration.

Symptoms of an acute pulmonary reaction usually appear hours or days after initiation of nitrofurantoin and include the sudden onset of fever, chills, myalgia, cough and dyspnoea (with or without cyanosis), eosinophilia and rales at the lung bases. Symptoms usually resolve rapidly after medication cessation, but more severe pulmonary reactions can develop if nitrofurantoin is reintroduced or inadvertently continued.

Rarely, nitrofurantoin is associated with acute liver toxicity. Cholestasis has been observed in adults, ranging in age from 30 to 65 years, who received therapeutic doses of nitrofurantoin for a period of 2 days to 5 months. Again, discontinuation of therapy usually results in resolution of symptoms.

Polyneuropathies have been observed more in females and in patients with renal failure, but has also been observed in patients with normal blood urea nitrogen and marginal renal functional impairment. Early signs such as paraesthesia should be promptly reported to enable early intervention and nitrofurantoin discontinuation.

Medsafe comment:

This review highlights the adverse reactions of concern with nitrofurantoin. These acute adverse reactions continue to be associated with short-term nitrofurantoin use and there should be consideration of these within patient information as part of the condition of supply.

As with the Holmberg study, it should be noted that the initial symptoms of a pulmonary reaction are similar to those of an infection (eg, fever). The Committee should consider how to alert consumers about taking medical attention.

4.4 Geerts et al. (2013)[7]

Due to the metabolism of nitrofurantoin, in patients with renal impairment the excretion of nitrofurantoin is decreased and effective urine levels may not be achieved. Additionally, the risks of adverse reactions are greater due to increased serum levels of nitrofurantoin.

An epidemiological study was conducted, with data obtained from the Dutch PHARMO Record Linkage System, to determine whether ineffectiveness and the occurrence of serious adverse reactions during nitrofurantoin treatment were depended on renal function.

One cohort consisted of female nitrofurantoin users with and without known creatinine values. The second cohort consisted of female trimethoprim users with and without known creatinine values. In the Netherlands the recommended nitrofurantoin course is 50 mg four times daily for five days. Ineffectiveness was defined as the start of a second antibacterial for treatment of urinary tract infection within one month after the start of a course of nitrofurantoin treatment.

Potential confounders such as age, duration of antibacterial treatment, use of blood-glucose lowering medicines, use of immunosuppressive medicines, use of urinary antispasmodics and medicines use in cognitive impairment were controlled for.

Table 10: Association between renal impairment and ineffective antibacterial treatment

eGFR (ml/min/ 1.73 m^2)	Second antibacterial, *n* (%)	Follow-up time (person-days)	Incidence density (per 1,000 person-days)	Crude HR (95 % CI)	Adjusted HR[a] (95 % CI)
Nitrofurantoin					
>80	291 (15.7)	49,241	5.91	1.00 (Reference)	1.00 (Reference)
50–80	314 (17.0)	48,068	6.53	1.10 (0.94–1.29)	0.92 (0.78–1.08)
30–49	35 (21.1)	4,191	8.35	1.41 (0.99–2.00)	1.06 (0.74–1.51)
10–29	6 (30.0)	456	13.16	2.12 (0.94–4.75)	1.57 (0.70–3.52)
<10	0 (0)	30	NA	NA	NA
Unknown	2,431 (13.9)	46,7318	5.20	0.89 (0.78–1.00)	0.90 (0.79–1.01)
Overall	3,077 (14.4)	569,304	5.40		
Trimethoprim					
>80	94 (16.0)	15,537	6.05	1.00 (Reference)	1.00 (Reference)
50–80	114 (19.1)	15,315	7.44	1.22 (0.93–1.60)	1.15 (0.87–1.51)
30–49	14 (18.9)	1,889	7.41	1.20 (0.68–2.10)	1.06 (0.60–1.88)
10–29	0 (0.0)	240	NA	NA	NA
<10	0 (0)	30	NA	NA	NA
Unknown	1,092 (16.4)	174,811	6.25	1.03 (0.84–1.27)	1.03 (0.83–1.27)
Overall	1,314 (16.6)	207,822	6.32		

HR, Hazard ratio; 95 % CI, 95 % confidence interval; NA, data not available

[a]Ajusted for age and use of blood glucose-lowering drugs

The overall incidence density for ineffectiveness in nitrofurantoin was 5.4 per 1,000 person-days compared with 6.3 per 1,000 person-days with trimethoprim (Table 10). Although there was a trend

[7]Geerts AFJ, et al. (2013). Ineffectiveness and adverse events of nitrofurantoin in women with urinary tract infection and renal impairment in primary care. *Eur J Clin Pharmacol* 69: 1701-1707

for higher incidence densities with declining renal function with nitrofurantoin use, the association was not statistically significant. There was no trend observed with trimethoprim use.

The risk of adverse events leading to hospitalisation was statistically significantly higher in nitrofurantoin users with renal impairment compared with those with adequate renal function (Table 11). Pulmonary reactions and blood dyscrasias were the reactions observed. The overall incidence density for serious adverse events was 0.02 and 0.01 per 1,000 person-days for nitrofurantoin and trimethoprim users, respectively.

Table 11: Association between renal impairment and serious adverse events

eGFR (ml/min/1.7 m^2)	Adverse event, *n* (%)	Follow-up time (person-days)	Incidence density (per 1,000 person-days)	Crude HR (95 % CI)	AdjustedHR (95 % CI)[b]
Nitrofurantoin					
≥50	13 (0.35)	332,399	0.04	1.00 (Reference)	1.00 (Reference)
<50	4 (2.14)	16,618	0.24	6.14 (2.00–18.83)	4.13 (1.31–13.09)
Unknown	17 (0.10)	1,567,746	0.01	0.28 (0.14–0.57)	0.35 (0.17–0.73)
Overall	34 (0.16)	1,916,763	0.02		
Trimethoprim					
≥50	0 (NA)	106,740	NA	1.0 (Reference)	1.00 (Reference)
<50	0 (NA)	7,470	NA	NA	NA
Unknown	8 (0.12)	598,572	0.01	NA	NA
Overall	8 (0.10)	712,782	0.01		

[a] Adverse events during subsequent hospital admissions within 90 days after the start of a course of nitrofurantoin treatment: pulmonary reactions (n=33) and blood dyscrasias (n=1). Adverse events after the start of a course of trimethoprim treatment: pulmonary reactions (n=8)

[b] Adjusted for age

Nitrofurantoin treatment was not significantly associated with ineffectiveness in women with urinary tract infection and moderate renal impairment, but was significantly associated with adverse events leading to hospitalisation.

Medsafe comment:

This study was included as renal impairment (< 60 mL/min) is a contraindication for nitrofurantoin use. Although ineffectiveness of treatment was not significantly associated with degree of renal impairment there was an increase in adverse events. Should the Committee consider reclassification of nitrofurantoin appropriate, the effects of renal impairment will need to be managed. The adverse events in this study were only those that led to hospitalisation, therefore the occurrence may have been underestimated.

5.0 OTHER INFORMATION

A review of the diagnosis and management of urinary tract infections in the outpatient setting determined that immediate antimicrobial therapy with trimethoprim-sulfamethoxazole, nitrofurantoin or fosfomycin is indicated for acute cystitis in adult women[8]. However, individual factors should be taken into account.

A Cochrane review also concluded that there were no differences observed between the classes of antimicrobials for treating acute uncomplicated urinary tract infection in women. Nitrofurantoin was

[8]Grigoryan L, Trautner BW, Gupta K. (2014). Diagnosis and Management of Urinary Tract Infections in the Outpatient Setting. *JAMA* 312(16): 1677-1684

included as one of the antimicrobials in this review[9]. A benefit of nitrofurantoin identified in this study was that it does not share cross-resistance with other commonly prescribed antimicrobials.

Reclassification of trimethoprim and nitrofurantoin was considered in the United Kingdom in 2009[10]. The reasons for rejecting the proposal appeared mainly related to the potential emergence of resistance to trimethoprim rather than to nitrofurantoin and the European Union directive that member states should not allow dispensing of antibiotics without prescription.

New Zealand antimicrobial resistance data from hospital and community laboratories as compiled by the Institute of Environmental Science and Research shows that nitrofurantoin resistance to *Escherichia coli* is low (see Appendix 1).

6.0 CONCLUSION

Despite the limited evidence for the safety of nitrofurantoin, likely due to the early discovery and approval of the antibiotic, the same adverse reactions continue to arise from nitrofurantoin use. These include acute hypersensitivity reactions that affect the skin (urticaria, rash) and the lungs (dry unproductive cough, dyspnoea), and gastrointestinal upset (nausea, vomiting).

It is noted within the submission for nitrofurantoin reclassification that the proposal is to widen the criteria to allow women who have had antibiotics within the last six months to receive nitrofurantoin if other criteria are met. Based on the available literature and the reports submitted to CARM, Medsafe recommends that the Committee should consider the frequency with which nitrofurantoin may be supplied by the pharmacist. This is not due to resistance issues, but rather that regular, intermittent use of nitrofurantoin increases the risk of hypersensitivity reactions, which may manifest particularly as acute pulmonary reactions.

There are a number of potentially serious adverse reactions associated with the acute use of nitrofurantoin. Should the Committee consider reclassification there should be consideration to providing nitrofurantoin in an approved pack, with a compulsory patient information leaflet that has been user-tested to ensure comprehension.

These reactions may be more likely to occur with the second or third use and may therefore be unexpected by the consumer. Information provided in the patient information leaflet should include signs and symptoms of potential adverse reactions such as shortness of breath/breathlessness, onset of dry unproductive cough and rash that may be red or itchy. In addition, the symptoms of these acute allergic reactions can be confused with those of infection. Medsafe strongly recommends that consumers should be provided with adequate, understandable information to alert them to these potential reactions and what to do should they experience relevant symptoms. Lastly, information should be included that symptoms can also occur after nitrofurantoin has been stopped or the course of treatment completed.

It would not be considered sufficient to provide oral information only, written information should be mandatory when supplying this antibiotic.

[9]Zalmanovici Trestioreanu A, Green H, Paul M et al. (2010). Antimicrobial agents form treating uncomplicated urinary tract infection in women. *Cochrane Database Syst Rev* 6(10): CD007182

[10]Dryden MS, Cooke J and Davey P. (2009). Antibiotic stewardship – more education and regulation not more availability? *J Antimicrob Chemother* 64(5): 885-888

Antimicrobial resistance data from hospital and community laboratories, 2013[1]

	Percent resistance (number tested [2])																
	amikacin	ampicillin	cefepime	ceftazidime	ceftriaxone/cefotaxime	cefuroxime/cefamandole	cephalothin	co-amoxiclav	co-trimoxazole	fluoroquinolone	gentamicin	imipenem/meropenem	nitrofurantoin	piperacillin-tazobactam	ticarcillin-clavulanic acid	tobramycin	trimethoprim
Acinetobacter species	2.1 (189)			7.2 (559)					7.2 (598)	2.5 (640)	1.9 (618)	2.3 (440)		4.6 (373)		1.4 (296)	
Citrobacter freundii [3]	0.0 (140)				26.6 (320)				12.9 (271)	4.2 (404)	7.1 (407)	1.1 (280)				5.0 (161)	
Enterobacter species[3]	0.1 (705)				29.3 (1491)				9.6 (1514)	2.2 (1993)	4.1 (1860)	0.4 (1348)				2.7 (739)	
Escherichia coli from bacteraemia	0.1 (759)	59.7 (1476)	6.7 (568)		6.2[4] (1148)	9.1 (1332)	26.7 (802)	14.8 (1442)		11.5 (1533)	8.5 (1686)	0.3 (1340)				3.9 (773)	
E. coli urinary	0.0 (10952)	50.3 (98683)			3.8[4] (55351)	5.8 (14188)	24.2 (9518)	7.7 (98489)	24.5 (13684)	7.9 (67758)	4.6 (29399)		1.3 (99411)			2.1 (8962)	26.2 (98127)
Klebsiella species from bacteraemia	0.0 (234)		11.4 (193)		17.2[4] (366)	20.3 (300)	29.9 (221)	13.4 (373)		8.4 (383)	12.5 (375)	0.0 (335)				4.3 (231)	
Morganella morganii [3]	0.0 (209)				7.8 (437)				20.7 (440)	7.6 (582)	16.3 (571)	0.3[5] (332)				4.2 (213)	
Proteus mirabilis	0.3 (640)	12.4 (3282)			1.5 (1309)	2.6 (1283)	4.0 (1277)	1.6 (3409)	12.3 (1312)	1.7 (1797)	3.5 (1876)	0.1[5] (1001)				1.5 (671)	
Pseudomonas aeruginosa	1.9 (1685)		1.4 (2655)	2.4 (8909)						6.9 (9589)	5.4 (8971)	5.3 (7388)		1.9 (6614)	12.5 (1323)	2.1 (3454)	
Serratia species[3]	0.3 (314)				10.2 (625)				5.6 (834)	6.9 (926)	1.5 (926)	0.2 (566)				3.4 (298)	

	Percent resistance (number tested [2])															
	amikacin	ampicillin	ceftriaxone/cefotaxim	clindamycin	co-amoxiclav	co-trimoxazole	erythromycin	fluoroquinolone	fusidic acid	gentamicin	methicillin/oxacillin	mupirocin	nitrofurantoin	penicillin	tetracycline	vancomycin
Campylobacter species							0.8 (238)	2.1 (236)								
Coagulase-negative Staphylococci (blood isolates)				30.4 (1006)		35.1 (1011)	50.0 (1160)	21.7 (577)		31.5 (980)	57.1 (1483)			86.4 (1258)	11.3 (707)	0.6 (669)
Enterococcus species		4.8 (13644)								27.6[6] (2589)			1.6 (11556)		73.3 (1303)	1.8 (4464)
Haemophilus influenzae (non-invasive)		23.1 (8388)			2.7 (8131)	30.1 (7815)									1.4 (6119)	
Moraxella catarrhalis		98.5 (390)					0.0 (151)								1.3 (154)	
Staphylococcus aureus [7]	0.2 (1774)			8.8 (80605)		1.4 (92298)	12.5 (93195)	6.0 (12056)	19.1 (11146)	0.9 (22498)	10.2 (110622)	9.3 (15047)		86.2 (96202)	2.0 (73874)	
Methicillin-resistant *Staphylococcus aureus*	0.0 (707)			16.6 (8138)		1.6 (8190)	24.9 (8191)	21.0 (3030)	47.3 (2528)	3.1 (3216)		10.8 (3247)			2.5 (7413)	
Streptococcus pneumoniae (non-invasive)			2.8[8] (321)			25.8 (2379)	20.1 (2904)							14.0[9] (2794)	19.1 (2396)	
Streptococcus pyogenes							2.6 (8127)							0.0 (5346)		

1 Data supplied by Aotea Pathlogy; Canterbury Health Laboratories; Greymouth Hospital laboratory; Hawkes Bay Hospital laboratory; Healthlab Kew; Hutt Hospital laboratory; LabCare Pathology, New Plymouth; Laboratory Services, Rotorua; LabPlus; Labtests; Medlab Central; Medlab Wairarapa; Medlab, Whanganui; North Shore Hospital laboratory; Northland Pathology; Pathlab Bay of Plenty; Pathlab Waikato; Southern Community Laboratories, Canterbury, Dunedin and Hawkes Bay; Taranaki Medlab; Tlab, Gisborne; Waikato Hospital laboratory; Wellington Hospital laboratory; and Whangarei Hospital laboratory.

2 Data presented only if available for ≥100 isolates.

3 These organisms usually have inducible cephalosporinases. Stably-derepressed mutants that produce high levels of cephalosporinase frequently occur.

4 5.2% of *E. coli* from bacteraemia, 3.0% of urinary *E. coli* , and 16.8% of *Klebsiella* from bacteraemia were reported to be ESBL producers.

5 Data presented for *M. morganii* and *P. mirabilis* is for meropenem.

6 High-level resistance.

7 Includes methicillin-susceptible and methicillin-resistant isolates.

8 Cefotaxime/ceftriaxone resistance (MIC ≥4.0 mg/L, CLSI interpretive standard for non-meningitis infections).

9 Penicillin resistance (MIC ≥2.0 mg/L, CLSI interpretive standard for oral treatment of non-meningitis infections).

Submission to Medicines Classification Committee in response to agenda item 6.1 of the 53rd meeting regarding the proposed reclassification of nitrofurantoin from prescription medicine to restricted medicine.

Submission from the Centre for Adverse Reactions Monitoring (CARM), New Zealand Pharmacovigilance Centre, March 2015.

CARM is the national centre for receiving, assessing and recording suspected adverse drug reactions reported by health care professionals and others throughout New Zealand. It is contracted by Medsafe, NZ Ministry of Health to perform this function.

We support Medsafe's submission and the interpretation of our data that the submission includes showing that acute pulmonary reactions to nitrofurantoin can occur with short term use and in the age group to which this reclassification submission applies. We are aware of the resistance profiles of trimethoprim and nitrofurantoin to bacteria causing acute urinary tract infection but we have concerns that there may be more use of nitrofurantoin than is necessary if the recommendations in the submission for reclassification are approved.

We were recently alerted to the problem of acute pulmonary reactions to nitrofurantoin by a respiratory physician who, together with colleagues, had become concerned about the number of patients admitted to hospital with serious pulmonary reactions to nitrofurantoin including patients who had only used nitrofurantoin for short periods. Our further investigation and discussion highlighted the increasing resistance to trimethoprim of organisms responsible for urinary tract infections and the low resistance to nitrofurantoin. Therefore, at the time that the Medicines Classification Committee publicised the application for nitrofurantoin reclassification we were in consultation with Medsafe and clinicians about what advice should be given to prescribers about the appropriate use of nitrofurantoin. This included raising awareness of the risk of short term as well as long term pulmonary reactions to nitrofurantoin, how they might present and how they might be avoided or minimised.

The evidence for recommending nitrofurantoin as a first line agent for the treatment of uncomplicated urinary tract infection in New Zealand is summarised in a 2013 Best Practice Journal article "Antimicrobial resistance in primary care".[1] This reports ESR data indicating that 24.4% of E coli isolates in 2011 exhibited resistance to trimethoprim compared with 1.1% for nitrofurantoin. The low resistance to nitrofurantoin is the reason it has been used for long term prophylaxis for some years. At present we have only been supplied with cumulative data across the country for bacterial resistance but the article suggests that it may be variable by region. The authors also observe that most women presenting with an acute uncomplicated UTI do not have their urine tested so we don't know what the resistance pattern would look like if urine specimens from acute uncomplicated cases at first presentation were tested. We also don't know how the clinical recovery rate correlates with the laboratory findings. For these reasons the use of nitrofurantoin, at least in some parts of New Zealand, may be increasing unnecessarily.

The problem of unnecessary use of nitrofurantoin may be compounded if this application for reclassification is approved. In the successful application for reclassification of trimethoprim, a cautious approach was taken in advocating that women who had received antibiotics in the previous six months, because they were more likely to have infection caused by resistant organisms, should be referred to their doctors. It is largely this gap which the applicants are now seeking to fill by the reclassification of nitrofurantoin. However, a general practitioner is likely to have details of the antibiotics previously prescribed, the indications, and the responses to treatment which might allow a more informed decision for the patient. They are also more likely to be aware of reduced renal function which is important in the prescription of nitrofurantoin.

In the Nitrofurantoin reclassification application p 12 paragraph 4, it is stated that Medsafe's Suspected Medicine Adverse Reaction Search (SMARS) database (1 Jan 2000 to late 2014) held 129 reports for nitrofurantoin with two deaths and for trimethoprim (including co-trimoxazole) 431 reports with three deaths. However, an analysis of the database for trimethoprim alone (without sulfamethoxazole) shows that the number of reports was 168 for this time period, including one

death which trimethoprim may have contributed to. It is important to compare the two first-line agents directly as trimethoprim/sulfamethoxazole is reserved as a second line agent.

In order to avoid or rapidly abort pulmonary hypersensitivity reactions it is suggested in Appendix 7 that a three day course of treatment for uncomplicated acute urinary tract infection may be appropriate. However, no evidence is supplied indicating that this treatment duration is likely to be effective.

We are also concerned about the clinical ability of pharmacists to recognise acute onset pulmonary events, or a history of these, and ensure that appropriate screening, advice on the potential for acute reactions and early appropriate intervention is initiated. Sensitisation can occur within 1-2 weeks of first exposure to nitrofurantoin and on re-exposure such patients can develop acute reactions within 2-10 hours.[2] This highlights the need to have clinical acumen for presentations that are often quite subtle and knowledge of the patient's nitrofurantoin history. It then also becomes critically important to ensure that the history of exposure to nitrofurantoin and the documentation of any adverse events are recorded in the patient's health care notes and reported to CARM to enable entry into the National Medical Warning System. Pharmacists prescribing nitrofurantoin are unlikely to be able to access a patient's existing history at the time of prescribing and this is compounded by the challenges of ensuring that prescribing history and adverse reactions are recorded in the patient's usual practice notes.

We certainly support the approach suggested by Medsafe to minimise the occurrence and extent of pulmonary reactions. However, as well as our clinical concerns, there are a number of questions that need to be addressed concerning nitrofurantoin use, including patterns of bacterial resistance with first presentations of infection prior to treatment and local bacterial sensitivities. We therefore consider reclassification inadvisable. The health care provider with the most background information about the patient would be the best person to prescribe for an uncomplicated urinary tract infection if trimethoprim is considered unsuitable.

References

1. Ikram R. Upfront: Antimicrobial Resistance in New Zealand: What is my role in primary care? Best Practice Journal 2013; 54**.** http://www.bpac.org.nz/BPJ/2013/August/upfront.aspx

2. Aronson JK., Meyler's Side Effects of Drugs,4, 15th Ed, Elsevier,2006

[redacted]

March 30, 2015

Andrea Kerridge
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MEDSAFE
Wellington 6011
Provided electronically to: committees@moh.govt.nz

Agenda for the 53rd Meeting of the Medicines Classification Committee

Dear Andrea,

Thank you for the opportunity to submit comments on the Agenda for the 53rd meeting of the Medicines Classification Committee. [redacted] would like to comment on Agenda item 5.3 Nitrofurantoin 50 mg solid dosage forms from the current Prescription-Only Medicine classification to similar qualifications as trimethoprim. Suggested wording being:

> a Prescription-Only Medicine except in medicines for oral use containing 50 milligrams per dose unit when sold in a pack of 20 solid dosage units to a women aged 16-65 years for the treatment of an uncomplicated urinary tract infection by a registered pharmacist who has successfully completed the New Zealand College of Pharmacists' training course in the treatment of urinary tract infections, where supply adhere to the screening tools approved by the Pharmaceutical Society of New Zealand.

[redacted] does not support the proposal to reclassify nitrofurantoin 50 milligrams per dose unit when sold in a pack of 20 solid dosage units and believe that the current medicine classification remains appropriate for the following reasons:

5-7 days dosage

- The Nifuran data sheet advises the dose of 50mg is to be taken four times daily for 7 days. [1]
- The proposed classification and BPAC guidelines provide for 50mg to be taken four times daily for 5 days.

Compliance

- It is well known that an inverse relationship exists between the number of daily doses and the rate of compliance. Claxten (2001) reported 1 dose/24 hours (OD) had a Mean Dose-Timing Compliance of 74%, compared to 1 dose/6 hours (QID) of only 40%. Simpler, less frequent dosing regimens resulted in better compliance across a variety of therapeutic classes [2].

Email: [redacted]
Telephone: [redacted]

- Short course regimens (up to 3 days) are desirable because of the improved compliance that they promote, their lower cost, and lower frequency of adverse reactions. Nitrofurantoin (50 – 100 mg four times daily) is unsuitable for short term therapy of acute uncomplicated cystitis. [3]

Resistance

- E. coli resistance to nitrofurantoin has been reported in a survey in Latin American hospitals where antimicrobials are readily available without a prescription. [4]
- The World Medical Association statement on resistance to antimicrobial drugs recommends national medical associations to urge their governments to require that antimicrobial agents be available only through a prescription provided by licensed and qualified health care provider. [5]
- There is a well-accepted inverse correlation between compliance and resistance [6,7] which underscores the Anti-Infective Sub-Committee (AISC) of PTAC below.

The formulation is not in line with PTAC direction

- AISC therapeutic group review included "The Subcommittee considered that it could be beneficial to have a long acting nitrofurantoin preparation".

We trust these comment will be helpful for the Committee's decision-making.

Kind Regards,

[redacted]

References:

1. Nifuran data sheet. Retrieved from http://www.medsafe.govt.nz/profs/datasheet/n/Nifurantab.pdf on 30 March 2015
2. Claxton, Ami J., Joyce Cramer, and Courtney Pierce. "A systematic review of the associations between dose regimens and medication compliance." Clinical therapeutics 23.8 (2001): 1296-1310.
3. Wagenlehner, F. M. E., and K. G. Naber. "Urinary Tract Infections: Uncomplicated." Retrieved from http://www.antimicrobe.org/e4a.asp on 30 March 2015
4. Gales, A.C.; Sader, H.S.; Jones, R.N. SENTRY participants group (Latin America). Urinary tract infection trends in Latin American hospitals: Report from the SENTRY antimicrobial surveillance program (1997–2000). Diagn. Microbiol. Infect. Dis. 2002, 44, 289–299
5. World Medical Association. WMA statement on resistance to antimicrobial drugs. 2008. Retrieved from http://www.wma.net/en/30publications/10policies/a19/ on 30 March 2015.
6. Niederman, Michael S. "Principles of appropriate antibiotic use." International journal of antimicrobial agents 26 (2005): S170-S175.
7. Food and Drug Administration. Combating Antibiotic Resistance (2015). Retrieved from http://www.fda.gov/ForConsumers/ConsumerUpdates/ucm092810.htm on 30 March 2015.

Email: [redacted]
Telephone: [redacted]

51st Meeting Medicines Classification Committee Item 6.1 Contraceptives.
Paula Avery
to:
committees
25/03/2015 06:08 p.m.
Hide Details
From: "Paula Avery" <averypaula@gmail.com>
To: <committees@moh.govt.nz>,
Security:
To ensure privacy, images from remote sites were prevented from downloading. Show Images

1 Attachment

Medsafe contraceptives.docx

25 March 2015

The Secretary
Medicines Classification Committee
Medsafe
Ministry of Health
Wellington

Dear Sir/Madam
Re: Agenda for the 51st meeting of the Medicines Classification Committee

Item 6.1 Oral contraceptives

Thank you for the opportunity to comment on this application proposal to allow accredited pharmacists to supply oral contraception to women aged 16 to 39 years in accordance with the approved protocol for supply.

I work as a GP at Papanui Medical Centre in Christchurch and I graduated from the University of Otago in 1996 and I am a Fellow of the Royal New Zealand College of GPs.

I oppose this proposal and I support the proposal that was forwarded by Jeanette McKeogh, the Group Manager Strategy and Standards, RNZCGP.

I think when our patients visit their GP for initiation or continuation of the pill, we have the opportunity to address their health in a more holistic way, than what can be achieved by our pharmacy colleagues. We are building up a relationship, and learning about our patients and having an opportunity to also provide preventive health care. Just about always when our patients come to see us, it is not just about them getting a prescription for the pill. It gives patients an opportunity to discuss what worries or concerns they have at the time, to find out how their home/life/school life is going and to build the foundation of a trusting relationship. In General Practice we are more able to provide continuity of care, and hopefully to be part of a person's support network. Obviously this is crucial when mental health issues arise as they often do in this age group. When talking about contraception we have the opportunity to talk about the patient's relationship as a whole and to try to ascertain if abuse is involved and to help patients avoid putting themselves at risk.

We have the benefit of having available their personal and family medical record to be able to inform patients better about which type of contraception may be more suitable and the pros and cons of each type for them. Also, to advise better about reducing the risk of disease transmission and to screen for sexually transmitted diseases and to investigate symptoms related to the reproductive system. When we see our patients for contraception requests we have the opportunity to offer cervical screening, check on smoking status, to offer smoking cessation, immunise, help with improving exercise and optimising patient's weight and to look at blood pressure control etc. Also, usually we address the other health issues a patient may have for example checking on asthma control, depression and anxiety management etc and whatever other health concerns a patient has at the time. Patients just about always want to talk about other health issues not just sorting out their contraceptive script.

We have available funding options to reduce financial barriers to patients who need to see us. In our practice we have free sexual health consultations for those under 21 years or the ability to use access funding to those where cost is a barrier.

I think if the Ministry of Health are wanting to improve health targets for the population, then patients need to be encouraged to see their GP.

Yours faithfully

Dr Paula Hanley

ALRANZ

Abortion Law Reform Association New Zealand Inc.

Introduction

The Abortion Law Reform Association of New Zealand (ALRANZ) was incorporated in February 1971 to seek the reform of the law in New Zealand so that a woman may choose whether to continue an unwanted pregnancy or obtain its termination. We assert that as the law stands it discriminates against women and does not conform to best medical practices. ALRANZ believes that abortion services need to be complemented by a comprehensive programme of education plus freely available contraceptive services. As an organization, we strive for legislative reform, while also engaging with the public to create a greater awareness of sexual and reproductive health and rights.

Reclassifying oral contraceptives from prescription medicine to restricted medicine

ALRANZ fully supports Pharmacybrands Ltd and Pharma Projects Ltd 's application to make oral contraceptives a restricted medicine. ALRANZ has long asserted that free and widely available contraceptives is key to ensuring women have the freedom to choose the timing, spacing and number of children.

We were disappointed to read the minutes from the 51st meeting, suggesting that the major problem with the application was the lack of collaborative work conducted with general practitioners. Our question is – what consultation has been done with those who need and access oral contraceptives? On average women will spend 25years of their life trying to control their fertility. Making this process easy should be a priority for all medical professionals – general practitioners, pharmacists, nurses, alike.

ALRANZ is not suggesting that integrated health services are not important; we have been arguing that exact point in terms of abortion services for 44 years, and we fully acknowledge the necessity of having the support of medical professionals. However, it is concerning to us that a medicine, which is key to a woman's sexual and reproductive health and with a high safety rating, has yet to be reclassified. Pharmacybrands and Pharma Projects Ltd are proposing a service that has been proven effective in other countries and would greatly improve many women's lives by offering them another option for accessing contraceptives.

ALRANZ would draw the Committee's attention to the most recent Abortion Supervisory Committee (ASC) report, which highlights two examples of why making oral contraceptives restricted medicine should be recommended: women seeking the removal to their implants because of side effects and the high percentage of women presenting for an abortion that are not using contraceptives.

Removal of LARCs

The ASC report noted that due to side effects of currently subsidized long-acting reversible contraceptives (LARCs), some women are choosing to have theirs removed:

While an encouraging number of women are choosing this method of contraception, we have received frequent anecdotal feedback from providers regarding the acceptability of the currently funded device in comparison to alternatives. A noticeable number of women who have had the currently funded implant inserted are having these removed due to side effects and there have been concerns regarding incorrect placement during insertion. Newer devices with more favourable side effect profiles and an improved mechanism that aids correct insertion are available internationally[1].

ALRANZ fully supports expanding access to a wider range of LARCs, but ultimately real choice means ensuring that all forms of contraception are available. Restricted access for oral contraceptives would provide an additional option or back up for women that are dissatisfied with their LARC.

Current contraceptive use

The ASC report outlines that 55% of women who presented for an abortion in 2013 were not using any form of contraceptive when they became pregnant, and a further 25% were using condoms only[2]. If contraceptives were available over the counter, how many women might get their pill while picking up condoms or choose on the day to go on the pill without the waiting time of seeing a doctor?

More specifically, the two largest age groups in the 55% were 20-24 (2412) and 25-29 (1663) year olds. The younger age cohort would certainly benefit from increased ability to control their fertility. Reducing unplanned pregnancies for these women are vital to increased educational and career opportunities.

The personal experiences of our membership would indicate that many would be grateful to have the option of going to their pharmacist for contraception. Most women will not choose to forgo other sexual and reproductive health services because they can easily see a pharmacist for birth control. Women will continue to seek out care for cervical screening and sexually transmitted diseases. However,

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[1] Report of the Abortion Supervisory Committee 2014, presented to House of Representatives pursuant to section 39 of the Contraception, Sterilization and Abortion Act, 1977: page 5.

[2] ibid: page 21 and 22.

many would contest the idea that having to schedule an appointment every six months is not onerous and costly, particularly for women with busy lives, childcare responsibilities, and/or those who live in remote areas.

Conclusion

To quote Dr. Daniel Grossman, a leading US obstetrician and gynaecologist[3]:

The prescription requirement is an out-of-date, paternalistic barrier to contraceptive use that's not evidence-based.

As Dr. Grossman indicates, making oral contraceptives a restricted medicine would move Aotearoa New Zealand into line with other Western countries.

ALRANZ encourages the Committee to consider the people who access oral contraceptives –women – and how easier access would improve their lives. Trust women to make the best reproductive decisions for themselves, including when and how to access contraceptives. Provide good information so women can be knowledgeable sexual beings and consumers, and enable them to freely and easily make the choices that are right for them. To our mind, this is what a patient centred approach to healthcare delivery means.

[3] British Medical Journal 2008; 337:a3044.

MEDSAFE -: 53rd Meeting of the Medicines Classification Committee 5th May 2015 Wellington NZ

Response regarding proposal to reclassify prescription products Desogestrel, Levonorgestrel, Norethisterone and Ethinyloestradiol <35 micrograms in the oral contraceptive pill (OCP) to restricted medicines available for sale over the counter at pharmacies and dispensed by trained pharmacists

Dear Sir/Madam,

This letter is in response to the request for Medicines Classification Committee review of a proposal to reclassify the above oral contraceptive medicines from prescription to restricted medicinal products[1]. We would like to raise some points regarding the above proposal which in our view are important to a positive benefit-risk profile of OCs in general.

While we do not disregard the important and critical role of the pharmacist in contraceptive counselling and even suggest widening of access to contraceptives be achieved through continued dispensing arrangements (as in Australia)[2], we would like to highlight a few points for consideration. We will discuss combined oral contraceptives (COCs) and progesterone only pills (POPs) separately as we believe they require distinct aspects to be counselled for to ensure safe and effective use.

COC as a class

Although the resubmission by the applicant to "Reclassify Oral Contraceptives NZ January 2015", argue that OCPs (and amongst them, certain COC formulations) are among the safest medications in the world, they are associated with rare, but serious side effects. With regards to the risk of VTE and ATE that is associated with the whole class of COCs, it is the overall risk increase with use of a COC compared to no-use which should drive the individual benefit-risk assessment. There is an ongoing scientific debate about differences in VTE risk between COC formulations depending on their progestin component.

The available evidence is conflicting, with some studies finding no difference between the progestins regarding risk for VTE[3,4,5] while others have highlighted an increased risk[6,7,8] It is

[1] Application to Reclassify Oral Contraceptives NZ January 2015

[2] Continued Dispensing of PBS Medicines in Defined Circumstances (continued dispensing) initiative - Australian Government September 2013- Department of Human Services/ Medicare Available at www.medicareaustralia.gov.au/provider/pbs/fifth-agreement/medication-continuance.jsp

[3] Dinger JC et al. The safety of a drospirenone-containing oral contraceptive: final results from the EURAS on OCs. Contraception 2007;75:344-354

[4]Seeger JD et al. Risk of thromboembolism in women taking EE/DRSP and other oral contraceptives. Obstet Gynecol 2007; 110:587-593

[5] Dinger Jurgen, Bardenheuer Kristina, Heinemann Klaas,Cardiovascular and general safety of a 24-day regimen of drospirenone-containing combined oral contraceptives: Final results from the internationactive surveillance study of women taking oral contraceptives, *Contraception* (2014) Article in Press (Article in Press Published Online 6th February 2014)

studies with a methodology that is less susceptible to bias and confounding which have consistently shown no difference between progestins. It remains conceivable that a differential risk observed in case control studies and data base linkage studies has been to a certain extent the result of bias and confounding[9]. The SOGC states that "Women using COCs should be advised that the highest quality evidence available at this time does not suggest a difference in VTE risk based on the type of progestin in the COC"[10].

The choice of COC formulations that are proposed to be made available in pharmacies in NZ is restricted to LNG-containing and NET-containing formulations based on the consideration of the authors that these formulations are safer in terms of VTE risk. While they quote a meta-analysis by Stegemann to show a 1.3 fold risk increase with so-called 3rd/4th generation formulations over so-called 2nd generation formulations, more consideration should be given to the fact that it is the 2-3 fold overall risk increase with CHCs as a class which is well recognized and most important for an individual patient's risk. We are concerned that making only a selective choice of COCs available in pharmacies would result in a public misconception of false security with these products. Awareness of the risk of VTE and ATE with this class of products is key to ensuring early recognition and appropriate treatment of thromboembolic events.

Thorough and comprehensive evaluation of the individual risk profile of a woman is one of the most essential elements in rendering CHCs safe to use. The company core data sheet (CCDS) for all Bayer COCs as well as the current update of the EU SmPC highlight that not only single risk factors may change the benefit-risk balance in an individual woman, but that there are also factors which may cumulatively enhance a woman's risk. The WHO-MEC and UK MEC for contraceptive prescribing refers to an extensive list of contra-indications and precautions[11] . A pharmacist would have to be appropriately trained in how to evaluate and assess a woman's individual risk factors and would have to be prepared to re-assess the risk profile regularly in order to maintain a positive benefit-risk profile for the use of any CHC.

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[6] Lidegaard Ø, Løkkegaard E, Svendsen AL, Agger C. Hormonal contraception and risk of venous thromboembolism: national follow-up study. BMJ 2009; 339: b2890

[7] Jick SS, Hernandez RK. Risk of non-fatal venous thromboembolism in women using oral contraceptives containing drospirenone compared with women using oral contraceptives containing levonorgestrel: case-control study using United States claims data. BMJ 2011;342:d2151.

[8] Parkin L, Sharples K, Hernandez RK, Jick SS. Risk of venous thromboembolism in users of oral contraceptives containing drospirenone or levonorgestrel: nested casecontrol study based on UK General Practice Research Database. BMJ 2011;342:d2139.

[9] Shapiro S, Dinger J. Risk of venous thromboembolism among users of oral contraceptives :a review of two recently published studies. J Fam Plann Reprod Health Care 2010; 36: 33–8.

[10] SOGC 19th February 2013 Position Statement Hormonal Contraception and risk of Venous Thromboembolism Available at http://sogc.org/media_updates/position-statement-hormonal-contraception-and-risk-of-venous-thromboembolism-vte/

[11] U.K Medical Eligibility Criteria for Contraceptive Use U.K MEC 2009 Faculty of Sexual and Reproductive Health Care Royal College of Obstetricians and Gynaecologists and WHO 2009 Medical Eligibility Criteria for Contraceptive Use Fourth Edition Department of Reproductive Health.

POPs as a class

The authors have proposed that the POP should also be available over the counter. With this type of hormonal contraceptive counselling on effective use is key for the benefit-risk profile of the products. The progesterone only pill is associated with less tolerance for delays in pill intake than COCs and even 1 missed pill might jeopardize reliable contraception, increasing the importance of missed pill advice for the patient[12].

GENERAL CONSIDERATIONS

Consensus has determined counselling is key for a positive benefit-risk balance for COCs as well as POPs. There are important elements that determine a successful counselling process. The setting within which patient consultation occurs is critical as many patients view a contraceptive discussion as extremely sensitive. This should include adequate privacy in a face-to-face setting. The HCP should engage in the discussion on contraceptive choice with background medical knowledge about the patient and with the capacity to discuss a full range of contraceptive options. A detailed history may need to be taken to ensure patients are not contraindicated to a particular contraceptive choice. Clinical judgement and skill must be employed to ensure the appropriate risk/benefit decision when a patient has a relative contraindication. Any HCP embarking on this complex counselling process needs to be appropriately trained.

The applicant emphasises the importance and rigor of training that will be provided to pharmacists, whom will provide the pill prescription service. The resubmission requires specially trained pharmacists to conduct comprehensive 20 minute consultations in the pharmacy prior to supply. The applicant needs to consider the practicality of the provision of 20 minute consultations within the retail environment. The comprehensiveness of the service needed would therefore be prohibitive for smaller pharmacies with only one registered pharmacist to offer the service. It can be unexpectedly burdensome for smaller pharmacies requiring additional personnel and private consultation area, away from the shop front and other customers. Unfortunately, this would result in only larger pharmacies to providing the service and also inconvenience for women, who now believe the pill is available over the counter at all pharmacies but may have to shop around several pharmacies to find a pharmacy offering the service. Therefore, the practicality of offering such a comprehensive clinical consultation in the retail environment may not enhance access as stated by the applicant.

A well-resourced business may need a booking system to provide this service to take one of the registered pharmacists out of the business for over 20 minutes to provide consultation and clinical examination in the form of BP monitoring and health screening. Therefore, this service may become very similar to getting a GP appointment but without the added and opportunistic benefits that can be provided by a more holistic women's health visit.

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[12] Chi I 1993 The Safety and Efficacy of progestin only oral contraception –an epidemiologic perspective Contraception 47(1) 1-21

The applicant also points out that the trained pharmacist will use a screening questionnaire to ensure that the woman is not contraindicated to the combined pill or POP. If the pill is not appropriate the pharmacist will refer to a GP but will be able to discuss other options. The pharmacist will ask her to abstain from sexual intercourse or use a barrier method until she is able to reach a GP and access another suitable option. However, pill prescription can be complex and we would argue that the UKMEC criteria guiding appropriate contraceptive selection for individual patients requires clinical training and an integrated understanding of the various clinical conditions and the severity of these conditions which can together mean that caution is needed when prescribing the combined pill or that the pill is contraindicated for the woman. A GP in this circumstance may have access to clinical notes and patient medical history, but may also be able to make decisions regarding more suitable options and provide them immediately to the woman without need for referral.

While we in principal agree to the necessity to provide easy access to reliable contraception a safe level of patient evaluation and guidance on proper use needs to be maintained. The continued dispensing arrangements as they are already implemented in Australia allow pharmacists to supply oral contraceptives when there is an immediate need for the medicine and the consumer cannot access a prescriber. This provision might allow to close a substantial gap in accessibility in New Zealand by giving the consumer greater access to the product if they cannot reach a doctor and thereby improving adherence and continuity of contraceptive protection.

Possible Public Health Benefits of the Contraceptive Consultation

The contraceptive consultation may allow opportunistic screening for breast and cervical cancer as well as the opportunity when discussing contraceptive methods to discuss barrier contraception and Sexually Transmitted Infection (STI) risk. It may also allow the primary care provider the ability to counsel the patient and promote behaviours to decrease infection risk[13]. With such high rates of chlamydia in western countries, opportunistic screening opportunities could provide enormous public health benefit. Indeed, Rose and colleagues in their research with young New Zealanders highlighted the preference of young people for routinely offered opportunistic chlamydia screening when visiting the doctor for other reasons[14].

[13]Petersen R et al Contaception 2004:69 213-217

[14] Rose S, Camille Smith M, Lawton B 2008 If everyone does it, it's not a big deal –Young people talk about chlamydia testing *NZMJ* 121 1271:33-42

Committee and Support Services
Product Regulation
Medsafe
Ministry of Health
Wellington

2nd April 2015

Dear Committee,

Re: The Reclassification of Selected Oral Contraceptives

(Application to Reclassify Oral Contraceptives, January 2015 by Green Cross Health and Pharma Projects Ltd).

Women's Health Action is a health promotion, information and consumer advisory service. We work with health professionals, policy makers and other not for profit organisations to inform government policy and service delivery for women. Women's Health Action is in its 31st year of operation and remains on the forefront of women's health in Aotearoa New Zealand. We provide evidence-based analysis and advice to health providers, NGOs and DHBs, the Ministry of Health, and other public agencies on women's health (including screening), public health, and gender and consumer issues with a focus on reducing inequalities. We have a special interest in breastfeeding promotion and support, body image and women's sexual and reproductive health and rights.

Thank you for the opportunity to comment on the proposed move to pharmacist supply of oral contraceptives.

General Comments:

Women's Health Action are also concerned with the health effects of high rates of unwanted pregnancies and terminations and we agree that access to affordable and available contraception needs to be improved especially for certain groups such as young and rural women. However, it is essential

that this is done safely and that patient rights to informed consent, privacy and equitable health care are protected. This includes the right to be seen by a properly trained health professional.

In 2014, Green Cross Health Ltd first applied to reclassify oral contraceptives. At this point questions were raised about integrated care, collaboration, pharmacist training, and pharmacist management of the patient. **We do not think the current application has addressed all these issues in sufficient detail and believe the application should be refused at this time and other options to provide safe affordable and accessible contraception to women and men be investigated.**

We recommend the following:

1. **Access to contraception**

We agree with NZ Family Planning (NZFP) that compared with pharmacists, Family Planning nurses are trained and well placed to prescribe contraceptive pills. A rapid way to improve access to contraception would be to immediately review the protocols for nurse prescribing through the Nursing Council to allow more primary care nurses to prescribe contraception. Promoting this role for Nurse practitioners in PHOs, particularly in areas without a Family Planning Clinic (FPC), or providing mobile family planning services in some areas, would also provide more affordable access and may be less daunting than a doctor's visit. There is also a need to provide culturally appropriate contraception and advice to some population groups.

2. **Addressing the cost of contraception**

We agree with NZFP that pharmacist supply of oral contraception will not necessarily reduce costs for contraceptive users and suggest there is no evidence that the priority groups for greater contraceptive access including young people, Māori and Pacific women and women with low incomes will necessarily benefit. More research and investigation is required in this area and in ascertaining the effects on health disparities.

3. **Addressing health equity**

The proposal may improve access for women living in areas with limited access to GPs and Family Planning clinics and potentially, youth. However, disparities are not necessarily addressed if the services provided are not of the same standard as provided by a GP, primary care nurse or Family Planning clinic.

4. **Ensuring Professional behaviour**

There have been media reports and we have received several anecdotal reports of Pharmacists taking a judgmental or inappropriate approach to providing emergency contraception including asking intrusive questions about sexual behaviour or failing to provide a private interview area. We are concerned there is no way of monitoring such incidents and none of the checks and balances in place for nurses and doctors. We have some concerns that busy pharmacists may not be able to find the time to undertake adequate assessment.

5. **Ensuring appropriate risk assessment**

AS NZFP have noted, family violence screening is now routinely practiced in Family Planning and most primary health care practices in New Zealand. Women who see pharmacists will miss out on this screening and intervention.

We agree a limitation of pharmacist-supply of oral contraceptives is the missed opportunity for opportunistic screening for a range of other health issues such as STIs, cervical smears, smoking cessation advice, alcohol advice, and discussion about general well being and for ongoing monitoring of any side effects.

Similarly, we also agree that it is common for patients and health professionals to find it difficult to assess certain risks. For example, if migraines, are the type that contraindicate a COC. We do not agree that women will necessarily recognise their contraindications or know the range of risk factors that should be assessed.

6. **Breast feeding**

There is clear evidence that some forms of contraception should not be used while breast-feeding. We are concerned that a Pharmacist may not be aware a woman is breast-feeding or may encourage stopping breastfeeding early to start on oral contraception.

Vested interests

General practitioners and Nurses provide medication for patients without a financial interest in the product. This will not be the case for Pharmacists. Health care consumer groups frequently identify cases of pressure/ inducements to prescribe on specialists by Pharmaceutical companies and pharmacists will not be immune to these and other commercial pressures.

If the proposal goes ahead we recommend the following:

1. **Training programmes**

A training programme as suggested by Family Planning lasting at least 2 days followed by regular update sessions. The programme must cover training in sensitive treatment of women seeking contraceptives, ethical issues, risk assessment and informed consent. It must include assessment of high-risk women to ensure they do not receive oral contraception when they are at high risk of complications, teaching of pill-taking so that women use the packets correctly and know what to do if they forget pills and information about STIs, use of condoms, cervical screening etc.

Pharmacists should be required to display evidence they have undertaken the programme.

2. **Age limit**

While we agree that young women have a right to contraception we believe this should be provided in the context of a full health assessment including monitoring of other issues such as family violence or coercion or STIs. Pharmacists should not be providing contraception to anyone under 16 or first time contraception to anyone under 18. We believe services should be free and access to family Planning clinics and GPs/nurses should be improved rather than substituting another potentially less adequate

service. We would not object to Pharmacy provision in the context of repeat prescription for women over 18.

3. **Staged approach**

We agree with NZFP there should be a staged approach, which includes auditing by a Doctor.

4. **COC and POPs**

We agree with NZFP that only the less risky POPs should be prescribed.

5. **Privacy**

That a fit for purpose designated private consultation room (i.e. not a store room or tea room) is provided for interview for any form of contraception including emergency contraceptives.

6. **Informed consent**

The information materials we have reviewed are not entirely objective, are too long and set at a high literacy level. A robust information and informed consent process must be developed that is set at a lower literacy level, is accessible and clear. Information must also be provided verbally, in a language the patient can understand.

7. **Collaborative agreements**

We agree with Family Planning and support the use of Collaborative Practice Agreements. The submission for the proposal mentions that many international pharmacist-supply programmes for oral contraception involve collaborative practice agreements where the pharmacist works with a doctor. We also agree initial auditing by a doctor, should be an essential part of any training programme.

We believe that the issue of collaborative practice raised by the Committee has not been adequately addressed by the new submission from Green Cross Health and Pharma Projects Ltd.

In conclusion, Women's Health Action agrees that access to contraception must be improved, especially for certain groups such as young women. However, we do not think that this proposal in its current form is a safe or effective way of achieving better access. Contraception should ideally be provided in the

context of overall health care, assessment of risk factors and ongoing monitoring. We would prefer to see increased family planning and PHO resources put in place

Thank you for this opportunity to comment on this proposal.

Yours sincerely

Dr. Sandy Hall

Policy Analyst
Women's Health Action.

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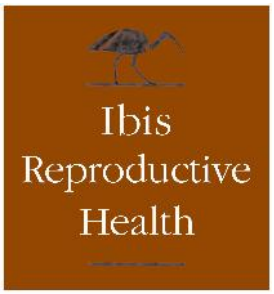

April 8, 2015

Medicines Classification Committee
Medsafe
PO Box 5013
Wellington 6145
New Zealand

Dear Committee Members,

I am writing this letter in support of the reclassification application submitted by Green Cross Health and Pharma Projects for several formulations of combined and progestin-only oral contraceptives. I am an obstetrician-gynecologist and researcher based in the United States, and I have conducted several studies exploring the safety and effectiveness of over-the-counter access to oral contraceptives, as well as women's interest in accessing this contraceptive method without a prescription. There is a growing body of evidence indicating that women can safely use oral contraceptives obtained without a prescription, and this model of pharmacy provision has also been studied in Washington State.[1] In addition, women want to access contraception without visiting a physician,[2] and studies suggest that uptake and continuation of effective birth control would improve if the prescription requirement were removed.[3,4] I believe the model proposed under this reclassification application would be safe and would offer more options for women seeking to avoid unintended pregnancy.

Our research has identified several concerns that both physicians and the general public raise when considering removing the prescription requirement. One is that women will avoid getting recommended preventive screening for cervical cancer or sexually transmitted infections (STIs). Our research of U.S. women obtaining oral contraceptives over the counter in Mexican pharmacies found that a high proportion—over 90%--reported having cervical cancer screening within the prior three years.[5] This figure is above the U.S. national average, and we found similar results for STI screening.

Another concern is that removing the prescription requirement will result in a lost opportunity to counsel about long-acting reversible contraceptive (LARC) methods, such as the IUD and implant. First, I understand that the protocol will include referrals to physician care for routine preventive screening, so women should continue to have contact with a clinical site. I also understand that written information would be provided to women in the pharmacy that includes an overview of contraceptives including LARCs to raise awareness of this option. Just because a woman starts the pill does not mean she cannot switch later to the IUD. Second, at least in the U.S., while we would like to believe that every physician—or even every family planning provider—counsels women about LARC methods, we know that is not the case. And finally, we have evidence that pharmacists can successfully refer interested women to obtain LARC methods, although few who present to a pharmacy seeking pills are interested in LARC.[6]

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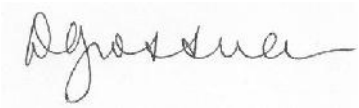
In addition to Washington State, California passed legislation in 2013 that will allow pharmacists to prescribe hormonal contraception (including a wider range than that being considered for reclassification in New Zealand), and the pharmacy protocols were recently approved by the California Boards of Medicine and Pharmacy. The program should launch later this year. While a few other countries, such as Tanzania and Vietnam allow at least some formulations of oral contraceptives to be provided by pharmacists who perform necessary medical screening,[7] New Zealand would be the first high-income country to implement this model nationwide. Mandating training for the pharmacists and using comprehensive screening tools and information sheets, which I have reviewed maximizes safety while improving women's access to contraception. The experience of New Zealand could serve as a model for other countries to learn from as they work toward addressing the problem of unintended pregnancy.

I would be very happy to answer any questions related to my research on this topic from committee members. Please let me know if you would like to schedule a time to talk by phone.

Sincerely,



Daniel Grossman, M.D., F.A.C.O.G.
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References

[1] Gardner JS, Miller L, Downing DF, Le S, Blough D, Shotorbani S. Pharmacist prescribing of hormonal contraceptives: results of the Direct Access study. J Am Pharm Assoc (2003) 2008;48(2):212-21; 5 p following 221.
[2] Grossman D, Grindlay K, Li R, Potter JE, Trussell J, Blanchard K. Interest in over-the-counter access to oral contraceptives among women in the United States. Contraception 2013;88(4):544-52.
[3] Potter JE, McKinnon S, Hopkins K, Amastae J, Shedlin MG, Powers DA, Grossman D. Continuation of prescribed compared with over-the-counter oral contraceptives. Obstet Gynecol 2011;117(3):551–7.
[4] Foster DG, Biggs MA, Phillips KA, Grindlay K, Grossman D. Potential public sector cost-savings from over-the-counter access to oral contraceptives. Contraception. 2015 Feb 27. pii: S0010-7824(15)00011-6. doi: 10.1016/j.contraception.2015.01.010. [Epub ahead of print]
[5] Hopkins K, Grossman D, White K, Amastae J, Potter JE. Reproductive health preventive screening among clinic vs. over-the-counter oral contraceptive users. Contraception 2012;86(4):376-82.
[6] Parsons J, Adams C, Aziz N, Holmes J, Jawad R, Whittlesea C. Evaluation of a community pharmacy delivered oral contraception service. J Fam Plann Reprod Health Care 2013;39(2):97-101.
[7] Grindlay K, Burns B, Grossman D. Prescription requirements and over-the-counter access to oral contraceptives: A global review. Contraception 2013;88(1):91-6.

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The Royal Australian and New Zealand College of Obstetricians and Gynaecologists

Excellence in Women's Health

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2 April 2015

Dr Stewart Jessamine
Chair, Medicines Classification Committee
Medsafe
Ministry of Health
Po Box 5013
Wellington 6011

Dear Dr Jessamine

I write on behalf of the New Zealand Committee of RANZCOG to provide feedback to the discussion about widening access to selected oral contraceptives. We know that this is on your agenda for the next Medicines Classification Committee, held on the 5th of May.

We supported the submissions considered in 2014 to reclassify four oral contraceptives that were listed under Item 6.1 on your agenda for the meeting held 8 April 2014.

In 2015, the NZ Committee remains strongly in support of any responsible development designed to improve access to quality contraceptive advice and service. Members are acutely aware that currently there are a number of barriers to access encountered by significant numbers of women. "Growing up in New Zealand" data shows that 55% of pregnancies to women living in the most deprived areas are unplanned.

To widen access in a responsible manner, NZ Committee members still believe that it would be effective to allow appropriately trained and accredited pharmacists working in suitable premises (ie with an appropriate, private space available for discussion and clinical checks) to write ***repeat*** prescriptions for the oral contraceptives.

We therefore support the proposed reclassification of those four medicines from prescription to restricted.

Please contact me if you require further discussion or information.

Yours sincerely

Dr Ian Page
Chair, New Zealand Committee of RANZCOG

The Royal New Zealand
College of General Practitioners

31 March 2015 Ref: JMK121-15

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Dear Andrea

Agenda for the 53rd Meeting of the Medicines Classification Committee

Thank you for providing the Royal New Zealand College of General Practitioners (the College) the opportunity to comment on the Agenda for the 53rd Meeting of the Medicines Classification Committee to be held in April 2015.

Introduction to general practice and the College
General practice is the specialty that treats patients: with the widest variety of conditions; with the greatest range of severity (from minor to terminal); from the earliest presentation to the end; and with the most inseparable intertwining of the biomedical and the psychosocial. General practitioners (GPs) treat patients of all ages, from neonates to elderly, across the course of their lives.

GPs comprise almost 40 percent of New Zealand's specialist workforce and their professional body, the Royal New Zealand College of General Practitioners (the College), is the largest medical College in the country. The College provides training and ongoing professional development for general GPs and rural hospital generalists, and sets standards for general practice. The College is committed to achieving health equity in New Zealand. To achieve health equity, we advocate for:

- A greater focus on the social determinants of health (including labour, welfare, education and housing).
- A greater focus on measures to reduce smoking and to increase healthy food options for low-income families.
- Health services that are better integrated with other community services.
- A review of the funding model for primary care to ensure that funding is targeted towards the most disadvantaged.
- Free primary health care for low-income families, because health inequities begin early and compound over the life course.

Submission

The College wishes to comment on the following three agenda items for the 53rd meeting of the Medicines Classification Committee:

- Item 5.6 Public consultation process
- Item 6.1 Nitrofurantoin – proposed reclassification from prescription medicine to restricted medicine (Green Cross Health Limited)
- Item 6.2 Oral contraceptives – proposed reclassification from prescription medicine to restricted medicine (Green Cross Health Limited)

Item 5.6 Public Consultation process

The MCC has asked for feedback on its consultation process. This is an area where the College has considerable concern. The current MCC process is opaque, and it is very difficult for an outsider to find out: what is being discussed by the MCC; the content of any supporting documentation; when and how to provide feedback; whether further opportunities for comment will be provided; and how to provide that further comment. It appears to the College that MCC processes are primarily used by those who have engaged regularly with the MCC over a number of years, and that it is very difficult for anyone unfamiliar with the MCC and its processes to provide input. The College has previously expressed concern with the public consultation process.[1]

The College is further concerned that there is also a strong risk of regulatory capture[2] in the MCC processes. On the one hand you have industry bodies that stand to benefit financially and substantially from MCC decisions, and which are therefore willing to invest considerable time and effort into making submissions, following debates and pushing for change. On the other hand you have the public interest, which, if it is represented at all, is represented by a diverse group of organisations – which usually: have a broad range of other interests and responsibilities; have minimal engagement because of competing priorities; have low awareness of MCC issues because of the agency's opaque and complicated processes; and stands to receive no financial or other benefit from the outcome of MCC processes.

The current agenda contains links to over 120 pages of submissions. These in turn reference other documents that need to be read to evaluate the submission. Often organisations commenting on proposals have limited resources and need to spread what resource they have between all the items on the agenda. There is the potential for multiple proposals to be made in the knowledge that organisations will be very stretched to make robust comment on them all.

Additional comment

An additional barrier to recent public consultation has been the blocking of emails containing links to the Medsafe website by the Barracuda email filter. The College is one of many organisations that use

[1] https://www.rnzcgp.org.nz/assets/Submissions/Agenda-for-49th-Meeting-of-the-medicines-Classification-Committee.pdf

[2] Regulatory capture is the process by which regulatory agencies eventually come to be dominated by the very industries they were charged with regulating.

this commercial email filter. We notified the MCC secretariat in September 2014 that we had not a received email notification of the agenda of the 52nd meeting, and hence had missed the deadline for responses. Initially we believed that the problem was with the College's email server and alternative arrangements were made – including arrangements by a College staff member to receive MCC emails via her home email address. We were unaware of a wider problem until we emailed four members asking for their comment and did not receive any responses. It appears likely that our communication with members was blocked by Barracuda because the emails contained a link to the Medsafe website. As a result of our investigations were able to notify Medsafe of the issue and they subsequently informed us that they have been successful in requesting that Medsafe be removed from the list of links blocked by the Barracuda email spam filter.

In our opinion, the current MCC consultation processes are not robust and present a high-risk of decisions that favour industry rather than the public interest.

Item 6.1 Nitrofurantoin – proposed reclassification from prescription medicine to restricted medicine (Green Cross Health Limited)

The RNZCGP is opposed to the proposed reclassification of nitrofurantoin.

Increasing antimicrobial resistance (AMR)

Antibiotic use in primary care makes a significant contribution to antimicrobial resistance (AMR).[3] As AMR grows, so does the threat to the routine treatment of common bacterial infections, treatment of severe infections and modern medical procedures. This threat is compounded by the lack of development of new antibiotics.

Increasing AMR is a worldwide problem. A high level of consumption of antibiotics is the main cause of high rates of antibiotic-resistant bacteria,[4] and antibiotic use in primary care makes a significant contribution. There is strong evidence of an association at the individual patient level between the prescribing of antibiotics in primary care and AMR at different sites, including the urinary and respiratory tracts and skin. Rates of resistance have been shown to be highest in the month directly after prescription and detectable for up to 12 months, thus increasing the population carriage of organisms resistant to first-line antibiotics.

Over recent years, New Zealand has seen an increase in the number of antimicrobial-resistant pathogens including community-associated methicillin-resistant Staphylococcus aureus, bacteria producing an extended spectrum beta-lactamase (ESBL) (e.g. E. coli and Klebsiella pneumoniae) and multi-resistant Neisseria gonorrhoeae.

The College is very concerned about the problem of antimicrobial resistance and had been working on this issue well in advance of the release of the current proposal around nitrofurantoin. The College will shortly be releasing a resource for GPs entitled "Increasing antimicrobial resistance – avoiding a post antibiotic era".[5]

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[3] Costelloe C, Metcalfe C, Lovering A, Mant D, Hay AD. Effect of antibiotic prescribing in primary care on antimicrobial resistance in individual patients: a systematic review and meta-analysis. BMJ. 2010 May 18;340:c2096.

[4] Thomas MG, Smith AJ, Tilyard M. Rising antimicrobial resistance:a strong reason to reduce excessive antimicrobial consumption in New Zealand. N Z Med J. 2014 May 23;127(1394):72–84

[5] https://www.rnzcgp.org.nz/policy-brief/

The proposed change to the classification of nitrofurantoin is likely to increase antibiotic use in primary care by the following means.

- An increase in the provision of antibiotics to women who do not require them. Not all women with the required two or more of the four symptoms of cystitis[6] will have a UTI and require antibiotics. In some cases symptoms resolve without antibiotic treatment.
- The provision of antibiotics to women whose symptoms are secondary to non UTI diagnoses.
- Ease of access to antibiotics is likely to result in a decreased emphasis on education on and use of strategies to prevent the development of a UTI.
- The lack of information available to GPs on which antibiotic has previously been dispensed by the pharmacist may lead to an increase in the use of non-first line antibiotics for UTIs.

Misdiagnosis

Members were aware of a number of conditions with symptoms which can mimic those of cystitis for example, STIs, genital prolapse, diabetes and ovarian cancer. There is therefore a genuine risk of misdiagnosis.

Fragmentation of care

As is the situation with the oral contraceptive pill (OCP), (discussed later) fragmentation decreases the quality of care. Good information flow mitigates some but not all of the negative effects of fragmented care. It is therefore important that if this proposal goes ahead the woman's GP is notified promptly of the provision of the antibiotic. This will be particularly important for those women who do not respond to the antibiotic supplied by the pharmacist, or are unable to tolerate it. Members commented that in their experience patients were more likely to have problems tolerating nitrofurantoin than trimethoprim.

Separation of prescribing and dispensing

There are good reasons for the separation of prescribing and dispensing. Pharmacist have a financial incentive to prescribe (or in this case supply) and there is a risk that this incentive may impact on their impartiality.

Lack of mandatory requirement for training, adherence to protocols or provision of a private area for consultation

We note that for pharmacists that have already undertaken training to supply trimethoprim it is proposed that no additional training be required to supply nitrofurantoin. Further training will be available but pharmacists are not required to undertake this.

We also note that although it will be suggested that pharmacists adhere to screening tools the submission states that "this is not essential" (Page 6).

The submission relating to trimethoprim included a requirement for a private area for consultation. This is not included in the requirements before supplying nitrofurantoin. If the MCC should make a decision to allow for pharmacist supply of nitrofurantoin then the requirements should include a private area for consultation.

The MCC has recently approved a number of medications to be classified as prescription medicines except where supplied by pharmacists meeting strict conditions. We are not aware of any monitoring of adherence to these conditions, and in this latest proposal adherence appears to have become optional. This is not appropriate.

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[6] Dysuria, urinary frequency, urinary urgency and suprapubic pain

The submission states that the reason for making this application is that under the current protocols for trimethoprim women who would otherwise be eligible for pharmacist supply of trimethoprim are ineligible if they have taken any antibiotics in the past 6 months. It seems that a more appropriate response would be simply to review the evidence base for the current protocols for trimethoprim. We would assume that a change in these protocols would require the approval of the MCC.

Item 6.2 Oral contraceptives – proposed reclassification from prescription medicine to restricted medicine (Green Cross Health Limited)

The RNZCGP continues to be opposed to the proposed reclassification of oral contraceptives.

Comparison with the 2014 Pharmacy Brands submission

The submission from Green Cross Health in support of reclassification appears to be in large part a copy of the 2014 submission. Key changes between the 2014 submission to the 51st meeting of the MCC and the current submission are;

1. The previous submission was made on behalf of Pharmacy Brands. They have since rebranded as Green Cross Health. Green Cross Health remains a body that represents retail pharmacy, and the commercial advantages to them of reclassification remain.

2. The proposed length of supply has been reduced from 6 months to 3 months (page 4 under pack size and other qualifications).

3. The paragraphs of supporting information have changed in some places. We note for example that the reference to the potential for pharmacist supply to decrease the rate of teenage pregnancy is no longer included. The recent increased availability of Long Acting Reversible Contraceptives (LARCs) has been credited with a significant drop in the teenage pregnancy rate.[7] As LARCs will not be supplied by a pharmacist this proposal may increase the likelihood that those young women for whom LARCs would be the most appropriate option would instead be supplied with the OCP. The OCP is unlikely to be as effective as LARCs in a teenage population.

It would have been helpful if there had been a list of changes to the proposal as there may be other changes that we have missed when comparing the two versions

Meeting with representatives of Green Cross Health and Pharma Projects

We appreciated the opportunity to meet with Dr Natalie Gauld of Pharma Projects and Alison van Wyk of Green Cross Health on February 19th. We also appreciated them making available copies of the draft checklists for OCP and POP and for giving us permission to share these with up to 6 GPs who would undertake to keep them confidential.

While the meeting allowed us to clarify some issues it did not allay our concerns around this proposal and in fact raised further concerns.

GP member feedback

Members felt strongly about this proposal and about 30 members provided feedback as a result of notification in ePulse (the weekly College electronic newsletter), and emails to members with an interest in relevant areas. Member response was overwhelmingly against this proposal.

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[7] http://www.radionz.co.nz/news/national/235957/steep-drop-in-teen-pregnancy-rates

Members were concerned that the underlying motive for the proposal related more to boosting retail pharmacy profits than to improving access to contraceptives.

In the College's response to the agenda of the 51st meeting of the MCC a range of concerns were expressed. Member feedback on this occasion reinforced those existing concerns and raised further issues. The 2014 response is included as an appendix to this response and should be considered along with this response.

The key concerns raised by members on this occasion are outlined below

Consultations for contraception

A consultation ostensibly about contraception is seldom limited to this issue alone. Depending on the individual patient and their situation and health needs it can include discussion of sexual health, STI testing, opportunistic risk screening[8], education, follow up of metal health or other health issues, or can provide an opportunity to engage with mothers regarding their around issues such as immunisation of their children. There is also the opportunity to discuss future child bearing plans and declining fertility with age, and to educate regarding pre conception care.[9]

A request for contraception requires a comprehensive discussion of the options available, assessment of possible contraindications, discussion of the risks and benefits of the various methods, and education on the use of the method selected. Particularly for young women a "pill consultation" often leads to a more complex consultation using the HEADSS[10] model.

Consultations relating to contraception provide an opportunity to engage with hard to reach members of the population who have other issues that require attention or follow up. These consultations also provide the opportunity to establish a therapeutic relationship which enables more effective and appropriate provision of future care whether or not this relates to contraception.

In the minutes of the 51st meeting it is recorded that "One Committee member stated that they acknowledged pharmacists were capable of managing the medicine but they were not convinced that pharmacists could manage the patient completely. The College endorses the view that pharmacists are not in a position to provide comprehensive ongoing care.

Fragmentation of care

An associated issue also mentioned frequently by members was the fragmentation of care that would result if this proposal went ahead. The more providers that are involved in the care of an individual, the more potential there is for error. The advantages of having a "medical home are increasingly acknowledged. Where a therapeutic relationship has already been established with the health provider this leads to increasing efficiency and quality of care.

Barriers to access to contraception

Several GPs commented that they did not consider that pharmacist provision was necessary to solve a problem with access to oral contraceptives. In New Zealand, unlike in many of the countries referred to in the submission, there is both a well-developed and subsidised primary healthcare system and in most cases pharmaceuticals are also subsidised. For many patients sexual health consultations are free, and for many others consultation fees are capped at a maximum of $17.50.

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[8] Cervical smears, smoking, alcohol, family violence, cardiovascular risk.

[9] For example check rubella immunity, advise re pre conception folic acid and iodine, and early pregnancy care.

[10] HEADSS stands for a number of categories (Home, Education, Activities, Drugs & Alcohol, Sexuality, Suicide)

On February 19 2015 TV1 news ran an item on the proposal for pharmacist provision of oral contraceptives. We presume that this was initiated by the organisations supporting the proposal. Viewer comments to the TVNZ website did not provide evidence of the existence or of a large demand for this service. On the contrary many voiced support for the OCP to remain available only on prescription.

Costs to women of pharmacist provision of the OCP

Members noted that a contraceptive consultation requires time and skill even when strictly limited to core contraceptive issues alone without opportunistic consideration of wider issues.
It is clear that pharmacists will need to charge the patient for providing a contraceptive consultation and if the woman is to be given adequate informed choice regarding contraceptive methods and appropriate education in their use, the consultation will take some time. As such there will be a commensurate cost for this consultation. This will act as a barrier to provision (as opposed to increasing access) and this barrier will be most significant for already disadvantaged women.

Effect on integration of care between pharmacists and GPs

Members commented on the negative effect that such reclassification proposals may have on the integration of pharmacists into primary health care teams. It was felt that such integration is challenging and that proposals driven by pharmacy retailer organisations have a negative effect on the climate for integration. GPs who contacted the College did not accept that the current proposal was driven by a need to improve access and were adamant that it would not improve the safety or quality of contraceptive care and would have a detrimental effect on holistic care and on access to other health care.

GPs commented that although the current financial climate was challenging for pharmacies reclassifications and hence changes to models of care should not be driven by the need to supplement current or future pharmacy income.

Access to patient records

Members expressed concern that pharmacists would not have access to the woman's medical record and would therefore need to rely on the information remembered and volunteered by the woman. This information can sometimes be inaccurate or incomplete. Although Testsafe and other similar programmes will mean that pharmacists are able to access some of the patient record for some women, safety issues due to incomplete or inaccurate information remain.

Conflict of interest

We note that the researcher engaged by Green Cross Health to manage the application to the MCC is a member of the Board of the Pharmaceutical Society. Under the proposal all responsibility for the content of the training for pharmacists wishing to supply the OCP would rest with the Pharmaceutical Society or its associated NZ College of Pharmacists. We consider that this conflict of interest should have been declared and appropriate mitigation proposed.

Feedback on the checklists for prescribing the POP and OCP

We are unable to provide specific feedback on the content of the checklists at this stage, although GPs who have had the opportunity to view the checklists have expressed some concerns to us about

them. If the check-lists are to be used, we would expect the College to be further consulted before implementation.

Minutes of the 51st meeting of the MCC

We were surprised to see the statement in the minutes:

> "The committee agreed that the risk: benefit profile of oral contraceptives was similar to other restricted medicines"

Especially, but not exclusively, when prescribed to women with contraindications oral contraceptives can lead to serious side effects.

We consider that the argument that a prescription medication could be reclassified because it is no more dangerous than something that is already classified as a restricted medicine is flawed. We are also aware that concerns have been expressed that medicines changes in New Zealand sometimes occur too readily. [11]

We hope these comments are of assistance to you. If you have any questions or comments, please do not hesitate to contact the College's policy team (policy@rnzcgp.org.nz).

Yours sincerely

Jeanette McKeogh
Group Manager – Quality, Research and Policy

[11] http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0119011 accessed 1/4/15

Appendix 1

Extract from the RNZCGP response to the Agenda for the 51st meeting of the MCC

Item 6.1 Oral contraceptives

The application proposes changes to the classification of oral contraceptive pill (OCP) ingredients Desogestrel, Ethinylestradiol, Levonorgestrel and Norethisterone. The submission in support of this proposal considers all of these together, as does our response. The proposed changes would allow accredited pharmacists to supply oral contraception to women aged 16 to 39 in accordance with the approved protocol for supply. Initiation of supply and continuation of supply would both be covered.

The College opposes this proposal. While our members frequently mentioned the need for women to have easy access to appropriate contraception and to minimise the number of unplanned pregnancies, the majority of respondents did not consider pharmacy supply as the only or the best method of achieving better access.

Issues raised by members include the following:

Initiating contraception and range of options

When done properly, initiating an OCP is a complex, time consuming consultation. Knowledge of the patient's previous medical, contraceptive and family history is very important. Women need to be informed of the options available and there needs to be a discussion of what might be appropriate in their particular circumstances and of the advantages and disadvantages of various options with respect to effectiveness, cycle control, possible side effects etc. The OCP may not be the best contraceptive option.

Pharmacists may refer women to a medical practitioner for other options. However, not all women will make that second attempt to obtain contraception. This is all the more likely in the case of women not entitled to free sexual health care from their GP who would then be required to make a second payment. This would effectively raise rather than lower barriers to access.

The submission implies that long acting reversible contraception (LARC) is an unpopular option but this is at variance with recent New Zealand reports of 'skyrocketing' rates of use of contraceptive implants with "13,500 women getting an implant last year" [12] LARC may well be a better option for many women, especially those at risk of missing pills, and many young people fall into this category. Rather than comparing the safety of the oral contraceptive with the health risks of pregnancy it may be more realistic to compare the risks of pregnancy when on the oral contraceptive with the risks of pregnancy on LARC.

Quality health care

Many of the women who see their GP for contraception rarely visit general practice. By visiting for contraception they have opportunity to become familiar with the practice and to develop a trusting relationship with their GP and practice staff. This assists patients in maintaining enrolment and their entitlement to a patient subsidy and in knowing how to access appropriate care rather than attending ED when unwell. Patients who have a general practitioner, or in American parlance have a 'medical home', are likely to receive better quality health care.

Particularly in the case of adolescents and younger women a request for contraception signals the onset of a major life-stage. A consultation with a GP provides an opportunity to enter into discussion over matters such as safe sex, risk taking and risk of partner violence and to screen for mental health issues. Our members expressed surprise that there should be a suggestion that this could be done properly in a pharmacy situation.

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[12] http://www.stuff.co.nz/national/health/8860716/New-contraception-slows-abortion-rates

The consultation also provides an opportunity to address general and women's health-related issues as well as preventative care. We know that brief interventions made by a GP can be very effective, as can opportunistic screening, and these are encouraged under current Ministry of Health policies. This proposal would lessen the opportunities for both to occur.

Sexually transmitted infection (STI) checks and cervical smears

The submission repeatedly states that STI checks and cervical smears are not necessary for contraceptive prescription. This appears to suggest that these are currently a barrier to the provision of contraception. We are not aware of any members refusing to prescribe contraception to any women declining to have a STI check or cervical smear, though GPs may note in the patient record that the patient had declined this examination. We would support contraception being prescribed if required.

Nonetheless, when women are seen by their GP there is the opportunity to encourage women to get STI checks and cervical smears while they are at the surgery. Should the proposal go ahead there is therefore a potential for both a reduction in cervical screening rates and an increase in the rates of STIs.

Fragmentation of care

It is well known that the more providers that are involved in the care of an individual the more potential there is for error. When pharmacists supply contraception the patient's full record will not be available and some information relevant to contraception may be too sensitive to be appropriate for a shared record. This will result in reliance on patients' recall of their medical, family and contraceptive history. However, patients' recall is often incomplete and they may not always disclose everything that is relevant.

There is also a likelihood that women will attend a different pharmacy each time they need a new supply of the OCP with a corresponding disruption in continuity of care.

Conflicts of interest

Financial incentives have the potential to influence practice. Not only may it be in the pharmacists' interest to promote oral contraception over other methods but they may also have an incentive to supply the brand with the largest mark-up. The separation of prescribing and dispensing is a safeguard of best practice. Although this proposal concerns supply rather than 'prescribing, the incentives to promote what can be sold at a profit are similar. While promotion of contraception generally is highly desirable, the same does not apply to the promotion of a particular type of contraception over options that may be more suitable and effective.

Pharmacist supply of oral contraceptives in emergencies

The effectiveness of the oral contraceptive is reliant on it being taken regularly. Women who run out of pills are therefore at risk of unintended pregnancy. It is important that women are able to access a supply of medication as soon as possible, even if it is at the weekend or if they are away from home. In New Zealand, women are already able to purchase the pill from a pharmacy in such circumstances. Pharmacists are allowed to provide an emergency supply of up to 72 hours of medication. Reclassification is <u>not</u> required to allow emergency supply as is suggested in the submission for reclassification.

Comparison with the supply of the emergency contraceptive pill (ECP)

While the College supports the supply of the ECP by suitably trained pharmacists there are significant additional considerations involved in the supply of the oral contraceptive pill. It is important the ECP is taken within a few hours of unprotected intercourse, and having it available from pharmacists facilitates this. By comparison, the OCP is not effective immediately and additional methods such as condoms should be used until it is.

BP threshold

Feedback from members also suggested that a lower BP than the suggested 140/90 should lead to referral to the GP for women requesting Ethinylestradiol containing medicines.

Training and 'screening'

It is not possible to comment on the adequacy of the intended training or of the methods of identifying women with contraindications – termed screening in the submission document, as the information about these has been withheld as being commercially sensitive.

Other comments

Rather than moving to pharmacist supply of oral contraceptives it may be preferable to further develop the role of the practice nurse prescribing under standing orders but still within practices. Here the prescribing nurse would have ready access to past medical history and screening information, and would be able to document what was prescribed and the required follow up directly into the patient's notes, and the GP would be able to be involved when necessary.

Should, however, the proposal be supported we consider it important that pharmacist supply should first be piloted. Evaluation of this pilot would reveal how effective and practical pharmacist supply of the OCP would be in the New Zealand context.

We would also emphasise the need for the GP to be informed of the pharmacist consultation, including which contraceptive was supplied and whether the women was advised to see a doctor for further investigations, screening or follow up. Communication with the GP should be the norm and the women should not have to request this (opt in). Women who are hesitant should be reassured that the GP will keep this information confidential and in particular will not inform her parents. If the woman does not have a GP then this is an opportunity for her to be assisted to locate one.

NZMA
New Zealand Medical Association

1 April 2015

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Agenda for the 53rd meeting of the Medicines Classification Committee

Dear Sir/Madam

The New Zealand Medical Association (NZMA) wishes to provide comment to the Medicines Classification Committee (MCC) regarding the agenda for the 53rd meeting scheduled for 5 May 2015. Our feedback is limited to items 6.1 and 6.2 plus general comment on the expansion of clinical services by pharmacy.

1. The NZMA is the country's largest voluntary pan-professional medical organisation with approximately 5,000 members. Our members come from all disciplines within the medical profession and include general practitioners, doctors-in-training, specialists, and medical students. The NZMA aims to provide leadership of the medical profession, and promote professional unity and values, and the health of New Zealanders. Our submission has been informed by feedback from our Advisory Councils (including our General Practice Advisory Council) as well as the Board.

Item 6.1 Nitrofurantoin – proposed reclassification from prescription medicine to restricted medicine (Green Cross Health Limited)

2. We note that item 6.1 entails the proposed reclassification of nitrofurantoin from prescription medicine to restricted medicine for the treatment of uncomplicated cystitis in women aged 16–65 years by pharmacists that have underdone the training that was required to be able to supply trimethoprim. The NZMA is opposed to this proposal for the reasons outlined below.

3. We are concerned that the proposal may exacerbate antimicrobial resistance in the community through injudicious overuse by pharmacy (partly as a result of diagnostic imprecision). Antibiotic resistance is already a growing problem in New Zealand.[1,2] We note that if adopted, the proposal would enable pharmacists to supply two of the most common antibiotics used as empiric treatment for suspected urinary tract infections (UTIs). This would leave only norfloxacin and antibiotics based on urine testing available for practitioners of diagnostic medicine to use, to make a difference, if trimethoprim and nitrofurantoin use (and resistance) increase. As part of the NZMA's overall concerns, our General Practice Council also considers that nitrofurantoin is generally not as well tolerated or safe as a three day course of trimethoprim.

4. Some women presenting with UTI-like symptoms in general practice actually have alternative diagnoses (eg, sexually transmitted infection). Some women may have cystitis but no infection. Accordingly, the diagnosis of UTI and the decision to initiate treatment with antibiotics (as well as the choice of antibiotic) are not always straightforward. We believe that these decisions are best determined by a doctor in a general practice setting. An additional important aspect of a consultation in general practice is that it affords an opportunity to address other aspects of a patient's health and well being, something that it is difficult to envisage taking place in a pharmacy setting.

5. The proposal will not enhance integrated patient-centric care and, rather, has the potential to fragment care. While the proposal alludes to 'the importance of informing the patient's doctor of a nitrofurantoin supply', our association has some reservations as to whether (and how) this will be implemented in practice.

Item 6.2 Oral contraceptives – proposed reclassification from prescription medicine to restricted medicine (Green Cross Health Limited)

6. We note that item 6.2 includes proposals for the reclassification from prescription medicine to restricted medicine for selected oral contraceptives to allow supply by a pharmacist who has successfully completed a training course for the supply of oral contraceptives and is complying with approved guidelines. The NZMA remains strongly opposed to these proposals for the reasons outlined below.

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[1] Thomas MG, Smith AJ, Tilyard M. Rising antimicrobial resistance: a strong reason to reduce excessive antimicrobial consumption in New Zealand.N Z Med J. 2014 May 23;127(1394):72–84. Available from: https://www.nzma.org.nz/__data/assets/pdf_file/0003/34662/content.pdf

[2] Williamson DA, Heffernan H. The changing landscape of antimicrobial resistance in New Zealand. N Z Med J. 2014 Sep 26;127(1403):41–54. Available from: https://www.nzma.org.nz/journal/read-the-journal/all-issues/2010-2019/2014/vol-127-no-1403/6315

7. We are not convinced that the requirement for a prescription constitutes a significant barrier to accessing oral contraceptives in New Zealand. Furthermore, we believe that any existing concerns about access to the oral contraceptive pill can be satisfactorily and safely addressed via a delegated collaborative model of prescribing, now available under the Medicines Amendment Act 2013.

8. One of the most important aspects of prescribing the oral contraceptive pill is the advice and counselling about its use and about sexual health in general, particularly for younger females. It is difficult to envisage how this can be done well in a pharmacy setting. It can sometimes be difficult even for experienced clinicians to broach sexual health when dealing with a young patient. In some cases, the patient will present asking for advice on contraception or sexually transmitted infections (STIs), but in the majority of cases, opportunistic intervention will be necessary. Yet on average, in our experience, teenagers are seen at general practice less than once a year. As such, the potential for opportunistic medical interactions, as well as the act of forming a therapeutic relationship with a medical practitioner at a time of personal change, is already low. It is still our view that the proposed reclassification would undermine the opportunity for opportunistic intervention and screening for at risk behaviours in an important patient group.

9. The use of oral contraceptives is also not without risks that must be carefully considered before they are used and during their use. For example, combined oral contraceptives increase the risk of stroke in women who suffer from migraines with aura. They should not be started by women of any age who suffer from migraine with aura.[3] Combined oral contraceptives also increase the risks of venous thromboembolism (VTE) and are contraindicated for women with a current or past history of VTE and best avoided for those at high risk.[4] Various drugs interact with oral contraceptives to potentially decrease their efficacy, and it is important that patients are fully aware of these. Before prescribing oral contraceptives, therefore, it is necessary to obtain a thorough medical history, including cardiovascular risk factors, concurrent medications, allergies, and health problems (past and current). In many instances, a physical examination may be indicated (eg, when there is a suspected STI). We are not convinced that the tick box checklists that pharmacists are supposed to use before supplying oral contraceptives as part of this proposal will necessarily capture the requisite information to ensure the safe use of these medicines.

10. Finally, we believe that the proposed reclassification of selected oral contraceptives from prescription to restricted medicines is likely to further fragment patient care with potentially serious consequences for patients, including unintended pregnancy or life-threatening adverse events. We note that the pharmacist checklist forms as currently structured require the patient to opt in to inform their doctor of supply, a requirement that is not conducive to genuine integration with primary care.

General comment

11. The NZMA has reservations that proposals seeking an expansion in clinical services by non-medical professions, including the two proposals discussed above, could undermine integration and compromise patient safety. We are also concerned about the underlying

[3] Roberts H. Combined oral contraceptive: issues for current users. BPJ April 2012(12):21–9. Available from www.bpac.org.nz/BPJ/2008/April/docs/bpj12_contraceptive_pages_21-29.pdf
[4] Ibid

drivers behind such proposals. We note that the submission in support of the proposal for the reclassification of nitrofurantoin states that "Pharmacy as an industry has become proactive, driving new initiatives." Our association has developed a position statement on the principles of workforce redesign,[5] which we suggest Medsafe refer to during consideration of the above (and subsequent) proposals. We attach a copy of this for the Medicines Classification Committee's and Medsafe's consideration. Specifically, we draw Medsafe's attention to principle #8 which is to 'Maintain or improve integration between involved medical services as well as integration of the patient within the healthcare system'.

We hope that our feedback to the Committee on these items is helpful and that our comments will be given careful consideration during its deliberations at the upcoming 53rd meeting. We look forward to learning the outcomes from this meeting.

Yours sincerely

Dr Mark Peterson
NZMA Chair

Attachments

1. NZMA. Principles of Health Workforce Redesign. February 2013.

[5] NZMA. Principles of Health Workforce Redesign. February 2013. Available from http://www.nzma.org.nz/__data/assets/pdf_file/0018/1458/Principles-of-Health-Workforce-Redesign-2013.pdf

Principles of Health Workforce Redesign

Approved February 2013

Preamble

The New Zealand Medical Association (NZMA) is fully aware of the need for healthcare reform driven by the twin factors of quality and efficiency. It is essential, however, to ensure that all healthcare reform (and workforce reform in particular) is developed, implemented and evaluated against broad core principles to ensure the safety of New Zealanders and the optimal delivery of healthcare to the population.
The NZMA has developed, in consultation with several other professional medical organisations, a set of core principles regarding health workforce redesign. Any proposed healthcare reform that compromises these core principles should clearly and openly acknowledge such a breach, and provide adequate rationale and justification for the deviation.

Principles

The NZMA believes that any proposed changes to workforce design should incorporate the following core principles:

1. Maintain or improve patient-centred access to the healthcare system, quality of patient care (including safety) and the patient experience.
2. Improve the involvement of Māori within the design and delivery of care, to ensure adherence to all the principles of the Treaty of Waitangi.
3. Respect all ethnic identities within the design and delivery of care.
4. Maintain or improve preventative care and population health.
5. Ensure equity in the access to and delivery of healthcare.
6. Incorporate/promote a whānau-centered approach to healthcare.
7. Maintain or improve patient-related communication flow including between healthcare professionals, as well as patient-driven care.
8. Maintain or improve integration between involved medical services as well as integration of the patient within the healthcare system.
9. Involve broad consultation with the key medical professional stakeholders and the public most affected by the change.
10. Ensure active clinical leadership in design, implementation and monitoring.
11. Ensure all reform is based on an assessment of the best available evidence/and or practice.
12. If pilot/demonstration schemes are considered, ensure these include requirements for thorough evaluation, including considerations of generalisability.
13. Facilitate rigorous evaluation and audit of systemic change.
14. Ensure adherence to a strong inquisitive research ethic and the facilitation of clinical and scientific research.
15. Clearly define the overall net cost and value to the healthcare system. Adequate rationale and possible concomitant disinvestment should also be considered.
16. Allow for dynamic change to ensure reform supports workforce responsiveness and adaptability.
17. Allow for ongoing healthcare education opportunities and the importance of continuing education as a core component of excellent healthcare delivery.

18. Ensure there is no net increased demand for limited health workforce resources without justifiable training, support or infrastructure for delivery.
19. Ensure that if role substitution or task delegation occurs, the delivery of healthcare is "fit for purpose" with all appropriate training, legislated authority and accountability for work delivery in-built.

Background

Views on the health system and the health workforce

Like all key stakeholders the medical profession, as an aggregate, desires that the New Zealand health system be: accessible, patient-centred, safe, and evidence-based. It should also be: integrated, culturally sensitive, fiscally responsible, cost effective, adaptive, equitable, and ethical. In addition, the system as a whole should be underpinned by an inquisitive research ethic and promote ongoing education of current and future health professionals. Clinical leadership should must be highly encouraged and form a core component of all healthcare reform and implementation.

As a consequence, in terms of the New Zealand health workforce, the NZMA promotes the profession's view that it should be highly skilled, fit for purpose, sustainable, team based, and flexible. Health professionals themselves need to have the interests of the patient at heart, be accountable and be valued/respected.

The role of the doctor within the health workforce

Following broad, multi stakeholder, pan professional engagement, the NZMA led the development of a consensus statement regarding the role of the doctor within the New Zealand health system.[1] This statement can be briefly summarised in the following key statements.

- Doctors regularly take ultimate responsibility for medical decisions and diagnoses in situations of complexity and uncertainty, drawing on scientific knowledge and principles, clinical experience, and well developed judgement.
- Doctors accept their ethical responsibilities to act in the best interests of their patients, and the population as a whole, and undertake this in a caring, compassionate, competent, and trustworthy manner.
- Doctors work in partnership with patients in the delivery of their healthcare and serve as advisors and interpreters in the pursuit of optimal health outcomes using evidence-based medicine and in accordance with available resources.
- Doctors work effectively as leaders. As members of healthcare teams, doctors recognise and respect the skills and attributes of other practitioners.
- Doctors are advocates for improved population health and health equity for all people.
- Doctors are committed to the spirit and principles of The Treaty of Waitangi, particularly as it relates to the attainment of health equity for Māori.
- Doctors have diverse roles, within and outside of the health sector, in the promotion and maintenance of both individual and population health.
- Doctors accept responsibility for maintaining the high standards of the medical profession to uphold the trust placed in them by patients and the community, and demonstrate this

[1] Role of the Doctor Position Statement, NZMA, 2011

through adherence to relevant declarations including the New Zealand Medical Association Code of Ethics and the Code of Health and Disability Services Consumers Rights.

Medicines Classification Committee
Ministry of Health

8 April 2015

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Dear Committee Members

Re: Submissions for reclassification – oral contraceptives and nitrofurantoin

I offer my full support to the proposed reclassifications of selected oral contraceptives and nitrofurantoin from prescription medicines to restricted medicines. My perspective is that of a pharmacy educator with a longstanding research interest in access to medicines and medicines reclassification.

Current pharmacy education and training provides students with in-depth knowledge of the pharmacology and clinical use of these medicines and with the skills to make assessments on their suitability for individual patients and to provide appropriate medication counselling.

During the Auckland BPharm programme, for example, students receive a considerable amount of training in physical assessment, screening and monitoring, and patient counselling. In respect of cardiovascular risk assessment, the following aspects are covered:

- Performance of health assessments related to cardiovascular risk factors including: Body mass index; Waist circumference; Blood pressure; Lipid levels; Glucose levels; Smoking status
- Gathering of pertinent patient information including past medical history, family history and smoking history
- Use of the New Zealand Cardiovascular Risk Assessment and Management Guidelines
- Assessment of cardiovascular risk factors and calculation of absolute cardiovascular risk
- Counselling and education of patients and/or caregivers on cardiovascular risk

These items are taught in a variety of settings, for example in pharmacotherapeutics workshops, pharmacy practice laboratories, communications workshops, ethics workshops, and for the physical assessments at the multidisciplinary Clinical Skills Centre (CSC). In Years 3 and 4 of the programme, students undertake modules in Clinical Skills run by the CSC.

By the time they graduate, students will have been assessed on measuring blood pressure using both sphygmomanometers and automated devices, and on their counselling of patients on the parameters and interpretation of blood pressure recordings. They will also be familiar with of a variety of point-of-care testing devices and their application. They will also have received extensive training in patient counselling throughout the programme, including the discussion of sensitive or potentially worrying information. Such counselling is framed in the context of clear ethical practice and moral reasoning and students are fully aware of requirements for confidentiality, patient autonomy, and so on.

In terms of the requisite knowledge base, as well as tuition in the individual disciplines of microbiology, pharmacology, pathophysiology and so on, students undertake clinical modules in both Infectious Diseases and in Women's Health, which cover the use of these medicines in depth. Our students also engage with other future health professionals, particularly nursing and medical students through a series of interprofessional learning activities. They are familiar and comfortable with their own and others' roles in the healthcare team and the process of referral to other health professionals.

I believe that these proposals would enhance the role of the pharmacist in the primary healthcare team and, rather than fragmentation of care as suggested by some opponents, it would lead to increased collaboration with general practice and other providers.

I have viewed the submissions for reclassification of selected oral contraceptives and nitrofurantoin and am very impressed with the case that has been made and the supporting evidence provided. I note that there has been wide consultation on these proposals and that that there is good support, including from within the medical profession. The protocols that have been developed are thorough and comprehensive, and the additional training required of pharmacists adds further weight to the submission.

Yours sincerely

Professor John Shaw
School of Pharmacy
The University of Auckland

[redacted]

2 April 2015 O1 02 01 03

Medicines Classification Committee Secretary
Medsafe, Wellington
via email: committees@moh.govt.nz

Dear Sir/Madam

MEDICINES CLASSIFICATION COMMITTEE
SUBMISSIONS TO THE 53rd MEETING AGENDA 5 May 2015

Thank you for the opportunity to submit comments on the Agenda for the 53rd meeting of the Medicines Classification Committee.

[redacted]

Regarding the agenda items for the above meeting of the Medicines Classification Committee, [redacted] would like to note the following comments for consideration:

5 MATTERS ARISING

5.2 Azelastine for nasal use

[redacted] **supports** the submission made by Medsafe to amend the classification wording of azelastine to:

- Prescription; except when specified elsewhere in the Schedule
- Pharmacy-only; **for nasal use in preparations containing 0.15% azelastine hydrochloride or less**; in topical eye preparations containing 0.05% or less

We are not aware of any evidence documenting specific risk of adverse effects with the slightly higher strength of the nasal spray; furthermore it would be sensible to harmonise the classification status with that of Australia which already lists the 0.15% strength as a pharmacy-only medicine.

5.3 Ketoprofen for topical use

[redacted] is concerned at the issues raised by the EMA documenting risk of photosensitivity reactions and co-sensitisation of ketoprofen. The concept of photosensitivity reactions is complex and something pharmacists have experience in counselling patients very carefully on, particularly when dispensing tetracyclines (especially for acne treatment) and methotrexate, where pharmacists utilise [redacted] Cautionary Advisory Labelling (CAL) system.

[redacted]

[redacted] CAL system advocates the use of a specific bright label warning for all medicines that carry a risk of photosensitivity-type reactions, along with accompanying verbal advice that advises patients to:

- Avoid sunburn and prolonged exposure in the sun (including sunbeds) while they are on sun-sensitising medicines (especially if other sun-sensitising medicines are being used concurrently);
- Be sensible in the sun by using sunblock and protective clothing and sunglasses
- Avoiding methotrexate specifically for at least four days after acute sunburn due to the known "solar burn reactivation" reaction.

This advice requires careful explanation and the expectation on pharmacists is that this is not simply a matter of label advice, but requires additional verbal counselling to ensure the patient fully understands the risk of the photosensitivity reactions, particularly considering the unique UV environment in New Zealand. Despite these warnings and reminders, patients do not always follow this advice and suffer the consequences of sometimes quite severe reactions. They have commented to pharmacists that they wish they had taken the warnings more seriously. Patients do not fully appreciate the seriousness of such reactions therefore written warnings alone are not adequate.

From the experience and advice pharmacists have in counselling patients on such reactions, and in considering the EMA report, [redacted] **supports** upscheduling topical ketoprofen to a pharmacy-only classification.

6 SUBMISSIONS FOR RECLASSIFICATION

6.1 Nitrofurantoin – proposed reclassification from prescription medicine to restricted medicine

[redacted] **supports** the proposal to reclassify nitrofurantoin to permit supply by pharmacists who have successfully completed the New Zealand College of Pharmacists training in the treatment of urinary tract infections.

The reclassification of trimethoprim to permit the supply by pharmacists without a prescription has proven to be extremely successful in terms of offering women the opportunity to receive the empirical antimicrobial treatment for an uncomplicated urinary tract infection. Pharmacists have completed the training developed specifically for this original reclassification and have consistently followed the approved assessment and management pathway process to accurately assess the patient and supply trimethoprim safely and appropriately.

The benefits of adding nitrofurantoin to the options available for pharmacists to treat uncomplicated UTIs are that an alternative and well-tolerated first-line treatment will be available for women who have contraindications to trimethoprim, and/or are unsuitable for trimethoprim supply, such as having received antibiotics in the preceding 6 months. Dosing of nitrofurantoin is considerably less convenient compared to trimethoprim at one 50mg tablet four times daily for five days, therefore the decision to supply nitrofurantoin would not be made lightly, and only after careful consideration by the pharmacist. Additional education advice and treatment algorithm around the use and choice of trimethoprim and nitrofurantoin would be made available to all pharmacists who have already successfully completed the College of Pharmacists Urinary Tract Infection training specified for trimethoprim; and for pharmacists newly completing this certification. Such education and tools will guide pharmacists through the assessment and decision-making pathway and the opportunity to supply trimethoprim or nitrofurantoin or refer is made clear.

6.2 Oral contraceptives – proposed reclassification from prescription medicine to restricted medicine

In our submission to the 51st Meeting of MCC, [redacted] indicated our support of the proposal to reclassify the listed oral contraceptives to Restricted Medicines. [redacted] continues to **support** the proposal and endorses the evidence and arguments for reclassification as outlined in the submission by Pharmacybrands and Pharma Projects. We reiterate our submission to the 51st meeting and repeat this below:

The function of a prescription generally serves two purposes, to permit the supply of a prescription medicine, and/or to attract a government subsidy through the Pharmaceutical Schedule (as applicable).

Women who visit a prescriber for a prescription of the oral contraceptive are generally not sick. They present predominantly to access funding of an effective contraceptive option they have personal control over (compared to condoms, for example), and as with all medicines supplied by a health professional, clinical risks and benefits will be assessed, and the medicine prescribed accordingly.

We note the considerable weight of expert opinion internationally expressing that the benefits of over-the-counter access to oral contraceptives outweighs the low risk. These expressions of opinion do not just come from individuals, but include *pre-eminent* professional colleges such as the Committee on Gynecologic Practice of the American College of Obstetricians and Gynecologists(ACOG)[(1)] and the Royal College of Obstetricians and Gynaecologists(RCOG)[(2)]. In considering over-the-counter supply of the oral contraceptive, we agree with the sentiment of the RCOG when they state:

> *"robust precautionary procedures and standards need to be in place to ensure patient safety"*

and that

> *"If dispensed by the pharmacist without prescription, information provided to women taking oral contraception needs to include contraindications, side effects and administration."*[(2)]

We also agree where they highlight issues regarding privacy and access to and the recording of personal data, and would assert that pharmacists manage their obligations under the Privacy Act 1993 and Health Information Privacy Code 1994 as part of their daily practice, and we do not see any difference in this should the oral contraceptive be made available as a pharmacist-only medicine. Proposed training and education of pharmacists will ensure all precautions and standards are met, and [redacted] has the support of the National Medical Advisor of Family Planning New Zealand to develop and deliver this (discussed below).

Safety

As the statement from the ACOG acknowledges, no drug or intervention is completely without risk of harm, and safety concerns about oral contraceptives frequently focus on the increased risk of venous thromboembolism. However,

> *"it is important to understand that the rate of venous thromboembolism for OC users is extremely low […] and to put this risk in context by recognizing the much greater risk of venous thromboembolism during pregnancy […] or in the postpartum period. Overall, the consensus is that OC use is safe."*[(1)]

The ACOG statement goes on to describe existing evidence demonstrating that women can self-screen for contraindications, however the present submission for reclassification is not asking for this and keeps the requirement for an educated health professional, the pharmacist, being involved in the screening for appropriate supply.

Accessibility

The burden on general practice to meet the health needs of the community is widely noted in both lay and professional media. The "New Zealand Health Survey: Annual update of key findings 2012/13" published by the Ministry of Health noted that

> *Twenty-seven percent of adults had experienced unmet need for primary care in the past 12 months. This includes unmet need for GP or after-hours services due to cost, transport or appointment availability. Women were more likely to have had an unmet need for primary care (32%) than men (22%)*[3]

Acknowledging that the Health Survey did not detail the clinical 'need' being sought, with this in mind, [redacted] considers that healthy women without the relevant risk factors should not need to visit their GP for the supply of their oral contraceptive, if they choose not to. This is an acceptable way of reducing unnecessary appointments, allowing GPs to focus on addressing those patients with health needs requiring medical assessment and management.

Furthermore, legislation currently permits a 6 month quantity of supply for the oral contraceptive. It is then extremely common that a considerable proportion of women do not then physically see their GP for repeat prescriptions, but will have these generated by request over the phone or by speaking with the practice nurse. This is a sentiment expressed by many women both to pharmacists, but also anecdotally by many of our female pharmacist colleagues. Significant periods of time will pass where a prescriber will not see a woman, fitting with our earlier stated recognition that these women are not ill. They do not need to see their GP for the sole purpose of prescribing of their oral contraceptive. With the described safeguards in place, women who choose to visit their pharmacist for supplies of their oral contraceptive will be continually screened for changes in risk and any women not meeting the strict criteria will be referred to their prescriber.

STIs and Women's Health Promotion

Pharmacists have been providing women with over-the-counter access to the emergency hormonal contraceptive pill (ECP) since 2002. A key function of this service, which is specifically expressed in the training and accreditation provided by [redacted], is the risk of sexually transmitted infections from unprotected sexual intercourse. Pharmacists discuss this with women during an ECP consultation and have information available to provide and recommend further investigation as appropriate. Likewise, condoms have been available from pharmacies for a considerable time, so discussions around STIs, risk factors and signs and symptoms requiring medical investigation are not new for the pharmacy profession. Furthermore it would be an ideal service to offer supply of an oral contraceptive at the time of an ECP consultation where appropriate.

[redacted] would not see any difference in sexual health promotion by pharmacists should they be able to provide the oral contraceptive over the counter, in fact this is likely to be enhanced. As would encouragement to participate in regular cervical screening by their GP – the more accessible and visible pharmacist would have a key role in further promoting this important public health issue.

Training and Professional Standards

[redacted] has a longstanding history of delivering education and training for pharmacists through the Emergency Contraceptive Pill training, and also through continuing education sessions on contraception and women's health. In considering a training programme to meet the needs of this reclassification, we have indications of support from appropriate medical specialists to develop education and training for pharmacists to ensure pharmacists' supply of the oral contraceptive is appropriate and safe. This will include full understanding of the risks and benefits of using the oral contraceptive, assessment and screening criteria (including blood pressure measurement, which is already conducted in many pharmacies), reasons for medical referral for those women who do not meet criteria for supply and determining the appropriate choice between pharmacist-available contraception and other available methods of contraception available that an individual may wish to consider. We understand that clear assessment and decision-support tools have already been developed by Green Cross Health and PharmaProjects to facilitate this process. Should the proposal to reclassify be accepted, [redacted] will work with these specialists to develop and deliver this training and could supply a detailed training proposal to MCC if requested.

As with the provision of all medicines and services by pharmacists, professional standards and legal and ethical obligations are expected to be observed. Any pharmacist acting outside of these would be subject to a formal Pharmacy Council or Health and Disability Commissioner complaints process. As has been demonstrated through a number of reclassifications from prescription to pharmacist-only medicine over the years, [redacted] does not expect anything other than the utmost professional duty of care by pharmacists when providing medicines.

7 NEW MEDICINES FOR CLASSIFICATION

7.1 Bilastine – proposed classification as a pharmacy-only medicine

[redacted] **supports** the proposed classification of bilastine as a pharmacy-only medicine in tablets containing 20 mg or less, when sold in a pack containing not more than 30 tablets, for the treatment of the symptoms of allergic rhinoconjunctivitis (seasonal and perennial) and urticaria.

One major review published recently concluded that bilastine has been shown to have comparative efficacy and tolerability to other second-generation antihistamines used as active comparators in phase III trials. However bilastine may have an advantages over cetirizine in having a significantly lower incidence of somnolence.[4] [redacted] considers bilastine to be appropriate for supply as a pharmacy-only medicine.

7.2 Otilonium bromide – proposed classification as a restricted medicine

[redacted] **supports** the proposal to classify otilonium bromide as a restricted (pharmacist-only) medicine and endorses the evidence and argument for this presented in the submission made to the Committee. Pharmacists practicing in the community are frequently approached by patients seeking options for the management of symptoms associated with irritable bowel syndrome (IBS). The availability of otilonium introduces a new possibility for people with IBS to obtain relief of the debilitating symptoms of cramping and spasm.

We agree with the approach in the submission that pharmacists could assess the symptoms of IBS through taking a targeted history to determine the suitability for otilonium treatment. While patients would be referred to their medical practitioner where appropriate 'red flags' were signalled, and/or if an initial trial of otilonium did not adequately address their symptoms. Wide accessibility of pharmacists could provide the first presentation for a potential

assessment of IBS, with a possible trial of treatment either successfully managing their symptoms, or the patient is referred for a more detailed medical assessment.

Proposed ongoing support of the classification of otilonium as a pharmacist-only medicine includes the development of an Irritable Bowel Syndrome patient Self-Care card to be added to the Pharmaceutical Society of New Zealand's Self Care Programme (consumer orientated leaflet). As well as an update of the currently available Continuing Professional Development programmes on IBS, it's assessment, management and treatment, with an addendum to include the place in therapy of otilonium.

There is building evidence showing that in addition to dietary/lifestyle interventions, a wide range of pharmacologic therapies which act directly on intestinal smooth muscle contractility, such as otilonium bromide, are well tolerated and effective for IBS; particularly in the relief of abdominal pain, severity of abdominal bloating and protecting from symptom relapse.[5], [6]

[redacted] therefore **supports** this proposal to list otilonium bromide as a pharmacist-only medicine.

Thank you for consideration of this submission.

Yours sincerely,

[redacted]

[redacted]

1. ACOG - Over-the-Counter Access to Oral Contraceptives [Internet]. [cited 2014 Mar 26]. Available from: http://www.acog.org/Resources_And_Publications/Committee_Opinions/Committee_on_Gynecologic_Practice/Over-the-Counter_Access_to_Oral_Contraceptives

2. RCOG statement on the widening of access to the Pill | Royal College of Obstetricians and Gynaecologists [Internet]. [cited 2014 Mar 26]. Available from: http://www.rcog.org.uk/what-we-do/campaigning-and-opinions/statement/rcog-statement-widening-access-pill

3. New Zealand Health Survey: Annual update of key findings 2012/13 [Internet]. Ministry of Health NZ. [cited 2014 Mar 25]. Available from: http://www.health.govt.nz/publication/new-zealand-health-survey-annual-update-key-findings-2012-13

4. Carter N J. Bilastine In Allergic Rhinitis and Urticaria. Drugs. 2012 Jun;72(9):1257–69.

5. Boeckxstaens G, Corazziari ES, Mearin F, Tack J. IBS and the role of otilonium bromide. Int J Colorectal Dis. 2013 Mar;28(3):295–304.

6. Clavé P, Acalovschi M, Triantafillidis JK, Uspensky YP, Kalayci C, Shee V, et al. Randomised clinical trial: otilonium bromide improves frequency of abdominal pain, severity of distention and time to relapse in patients with irritable bowel syndrome. Aliment Pharmacol Ther. 2011 Aug;34(4):432–42.

PHARMACY GUILD OF NEW ZEALAND

2 April 2015

Advisor Science (Secretariat for MAAC & MCC)

Product Regulation

Medsafe

Sent via email to: committees@moh.govt.nz

Dear Andrea

RE: AGENDA FOR THE 53rd MEETING OF THE MEDICINES CLASSIFICATION COMMITTEE

Thank you for making available the agenda for the 53rd meeting of the Medicines Classification Committee (MCC), to be held on Tuesday 5 May 2015, and for the opportunity to provide feedback on the agenda.

The Pharmacy Guild of New Zealand (Inc.) (the Guild) is a national membership organisation representing the majority of community pharmacy owners. We provide leadership on all issues affecting the sector.

Our feedback covers seven agenda items. These are:

- Agenda item 5.2: Azelastine for nasal use
- Agenda item 5.3: Ketoprofen for topical use
- Agenda item 5.4: Omeprazole – proposed reclassification from pharmacy-only to restricted medicine
- Agenda item 5.5: Paracetamol in combination with phenylephrine
- Agenda item 6.1: Nitrofurantoin – proposed reclassification from prescription medicine to restricted medicine
- Agenda item 6.2: Oral contraceptives – proposed reclassification from prescription medicine to restricted medicine
- Agenda item 7.2: Otilonium bromide – proposed classification as a restricted medicine

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Each of these agenda items is discussed below.

Agenda item 5.2: Azelastine for nasal use

The Guild **supports** the submission by Medsafe requesting confirmation that the pharmacy-only classification of azelastine hydrochloride remains appropriate when present in nasal preparations at 0.15% w/v.

We agree that the pharmacy-only classification for azelastine hydrochloride for nasal use should be clarified. It is important that medicine classifications include a strength limit. This makes the classification explicit and removes any confusion. We suggest the wording of the pharmacy-only classification should be "for nasal use, in preparations containing up to 0.15%".

Agenda item 5.3: Ketoprofen for topical use

The Guild **supports** a reclassification of ketoprofen for topical use from general sale medicine to an upscheduled classification.

We agree with the European Medicines Agency (EMA) review that further safety recommendations should be applied to ketoprofen for topical use to minimise the risk of adverse skin reactions. In a French study[1] the treatment with ketoprofen topical gel was over a period of about seven days, and the appearance of the side-effect was sometimes quite delayed relative to discontinuance of treatment. Although the rate of side effects was low, reactions were severe in 40 per cent of cases. Side effects were often related to sun exposure or occlusive dressing. For these reasons our recommendation would be that this medicine is reclassified as pharmacist-only medicine to ensure that every patient considering using this medicine receives a pharmacist consultation. This is of particular importance in a country such as New Zealand where sun exposure during summer months is high.

At minimum we believe that this medicine should be classified as pharmacy-only. Patients receive valuable advice in a community pharmacy as to the use of medicines and the potential for side effects.

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[1] Baudot S, Milpied B, Larousse C. *Cutaneous side effects of ketoprofen gels: results of a study based on 337 cases.* Therapie. 1998 Mar-Apr 53(2): 137-44.

Agenda item 5.4: Omeprazole – proposed reclassification from pharmacy-only medicine to restricted medicine

The Guild **strongly supports** the proposed reclassification of omeprazole from pharmacy-only medicine to restricted medicine.

In our submissions to the agendas of both the 51st and 52nd meetings of the MCC, we expressed the many concerns of our community pharmacy members regarding the potential lowering of classification for omeprazole. The safety concerns we expressed at that time included inappropriate and over use of this medicine, use in children and babies, the risk of hip and wrist fracture in patients taking this medicine long-term and the link between long-term use of proton-pump inhibitors with an increased risk of infection with Clostridium difficile. We believe these safety concerns alone are sufficient to warrant the reclassification of omeprazole to restricted medicine.

While the report from Medsafe's Pharmacovigilance Team draws no strong conclusions as to the safety concerns regarding omeprazole interactions, nine drugs have been listed as having clinically significant interactions with omeprazole. Several of these medicines, in particular digoxin, would be considered to be commonly prescribed. We ask that information regarding those interactions that have been found to be clinically significant be circulated by Medsafe to prescribers and pharmacists to improve the safety of omeprazole prescribing and we encourage you to reconsider reclassifying omeprazole as a restricted medicine.

Agenda item 5.5: Paracetamol in combination to phenylephrine

The Guild is pleased to see the MCC will revisit their decision made at the 52nd meeting to not reclassify paracetamol in combination with phenylephrine.

In our submission to the agenda for the 52nd meeting we expressed concern regarding the potential for patients to suffer from cardiovascular side effects due to the interaction between paracetamol and phenylephrine resulting in a high effective exposure to phenylephrine.[2]

It appears that further information has become available from additional studies that the interaction between paracetamol and phenylephrine has potential safety issues. We would strongly encourage the MCC to err on the side of caution and reclassify these medicines in the interests of public safety. A pharmacy-only classification is good middle ground between open seller and pharmacist only medicine for these popular cold relief medicines. This will provide a level of comfort regarding the sale of these medicines, and

[2] Tark, B. E et al, *Intracerebral Haemorrhage Associated with Oral Phenylephrine Use: A Case Report and Review of the Literature,* article in press.

ensure that patients are screened as to the appropriateness of using this medicine with their particular health conditions, and to recommend an alternative should the patient be found to have cardiovascular risks.

The comments received by the MCC against the reclassification included the view that the safety concern is theoretical and the submission for reclassification was based on a single study. Now that these same concerns have been raised by further studies it is timely to reconsider the recent recommendation.

Agenda item 6.1: Nitrofurantoin – proposed reclassification from prescription medicine to restricted medicine

The Guild **strongly supports** the proposed reclassification of nitrofurantoin from prescription medicine to restricted medicine.

Pharmacists who have completed the trimethoprim training have been providing female patients aged 16 to 65 years with this antibiotic treatment for uncomplicated urinary tract infections since its reclassification in 2012. The treatment of this infection is now something the majority of pharmacists are familiar with and are able to manage.

There is a very real difficulty at the moment where a pharmacist is unable to supply trimethoprim if the patient has had treatment with an antibiotic in the last six months. The pharmacist must refer the patient to the doctor for treatment. This typically results in treatment delays and places an unnecessary burden on an already over-burdened general practice. The simple solution would be to have an alternative medication available for the pharmacist to provide, and this proposed reclassification would support that need and ensure patients have the option to be treated immediately when they present in the pharmacy. The advantage of nitrofurantoin is that there is low bacterial resistance to it, and the most common bacterial cause of cystitis, *E. coli,* is very susceptible to this drug.

We are aware of the concerns regarding the side effects of nitrofurantoin, in particular the potential for lung injury. Nitrofurantoin has the potential to induce both acute and chronic pulmonary toxicity. While this is a significant concern, and should not be downplayed, pharmacists (like other health professionals) are ethically obliged to keep up to date with changes in risk and effectiveness profiles of medicines. Nitrofurantoin is not new to pharmacists as they have been dispensing prescriptions for this medicine for many years. Pharmacists should be well versed in the risk and effectiveness profile of nitrofurantoin whether dispensing the prescription medicine or providing the medicine as a pharmacist-only medicine should the medicine be reclassified.

We note that the submission request for reclassification is for "prescription only except in medicines for oral use containing 50 milligrams per dose unit when sold in a pack of 20 solid dosage units to a woman aged 16-65 years for the treatment of an uncomplicated lower urinary tract infection by a registered pharmacist who has successfully completed the New Zealand College of Pharmacists' training course in the treatment of urinary tract infections, where supply adheres to the screening tools approved by the Pharmaceutical Society of New Zealand". We would support this however we contend that all practising pharmacists are bound by the Pharmacy Council Competency Standards[3]. For pharmacists working in community pharmacy this includes supply and administration of medicines within the following standards:

- O3.4.1 Makes clinical assessment of the appropriateness of the medicines for a specific patient in order to administer it or to supervise the patient self-administering,
- O 3.4.2 Follows relevant policies, procedures and documentation requirements for administration of medicines
- O 3.5.1 Assesses patients' needs and knowledge of prescribed medicines, including Pharmacist Only medicines, to identify when additional information and education is required.
- O 3.5.3 Provides the patient with sufficient information to ensure the safe and proper use of medicine(s), including effective use of devices.

Any pharmacist adhering to the Council Competency Standards will therefore ensure that they are prepared to manage and minimise the clinical risks related to the use of nitrofurantoin. For this reason we believe that more appropriate wording for the Medsafe reclassification could be "restricted medicine: for oral use for the treatment of uncomplicated urinary tract infection, in medicines containing 50 milligrams per dose, when sold in packs of not more than 20 dosage units".

We are aware that excellent materials have been developed (including those developed by Green Cross Health Limited) that will support the pharmacist in the treatment of UTIs, the supply of nitrofurantoin and the referral of high risk patients. We commend these materials. Competent practising pharmacists will ensure that they have access to materials such as these or similar materials to support their treatment decisions and reinforce their advice to patients.

It is clear that there is significant public need for treatment of uncomplicated UTIs in the community. Feedback from our member pharmacies indicate that the reclassification of

[3] Pharmacy Council of New Zealand Competence Standards for the Pharmacy Profession. http://www.pharmacycouncil.org.nz/cms_show_download.php?id=504

trimethoprim has allowed pharmacists to address this need. One rural pharmacy on the West Coast for instance reported an average of 70 trimethoprim consultations per year.

One of the rate-limiting steps for the supply of trimethoprim has been the upper age limit of 65 years. Pharmacies have reported that healthy, fit, female patients over 65 years of age are the most common group of patients with UTIs that are referred on to the doctor. The reclassification of nitrofurantoin is designed to reduce unnecessary load on GPs. The submission for the reclassification of nitrofurantoin has suggested this same upper age limit of 65 years. We suggest an upper age limit of 70 years may be more appropriate.

Agenda item 6.2: Oral contraceptives – proposed reclassification from prescription medicine to restricted medicine

The Guild **strongly supports** the proposed reclassification of certain oral contraceptives from prescription medicine to restricted medicine.

We support the submission provided by Green Cross Health Limited and believe it shows a model of care for the supply of oral contraceptives that provides considerable safety, ensures all women will talk to a health professional, and provides a very integrated approach with referral to doctors at many steps.

In the United States, California has passed legislation that has opened up the availability of OCs without a prescription. As well as supplying oral contraceptives, this legislation allows for the provision of transdermal, vaginal and depot injections as forms of self-administered hormonal contraception. The protocol for supply includes a clear list of conditions that must be met before the supply can be made by the pharmacist. This includes the pharmacist providing a self-screening tool to the patient, which is then reviewed and clarified by the pharmacist. The pharmacist must measure and record the patient's blood pressure, and ensure that the patient is trained in how to self-administer the medicine. The pharmacist must counsel on dosage, effectiveness, side effects, safety and the importance of receiving the recommended health screenings such as smear tests. The patient must be informed that hormonal contraception provides no protection against sexually transmitted infections (STIs). The patient must be referred to a primary care provider or nearby clinic if it is found that it is not appropriate to provide the patient with contraception at that time. If the supply is made, the pharmacist must notify the patient's regular prescriber. To undertake the supply, the pharmacist must have completed a one-hour certified training.

In Canada, pharmacists are able to use their judgement as to whether to prescribe a medicine to a patient for up to three years of treatment. They are able to prescribe

prescription drugs (apart from Controlled Drugs) that are within their scope of practice, subject to federal and provincial regulations. They are able "to prescribe drugs for minor self-diagnosed or self-limiting ailments; monitor and authorize refills of existing prescriptions; modify and adapt a prescription to alter dose, formulation, regimen, or duration; complete missing information on the prescription; and provide emergency supplies of a prescribed medication to a patient"[4].

These examples illustrate how other countries are utilising their pharmacist workforce to take the pressure off their general practitioners, eliminate inefficiencies in community pharmacy and provide a convenient, front-line health service to the public. Pharmacists overseas are playing an increasingly important role within primary health care teams, working with patients to ensure they are using medications appropriately. There is an international trend of enabling safe prescription medicines to be supplied by pharmacists. Oral contraceptives are safe medicines and there is no reason to not make them more accessible for New Zealand women.

One of the main concerns raised by the MCC about the initial submission on this reclassification was the apparent lack of integrative approach. We contend that pharmacists are already working collaboratively with GPs in many situations. We are aware for instance of a pharmacy where the local general practice refers patients exhibiting cystitis symptoms to the pharmacist, to free up time for the GP. Another general practice refers tourists requesting the emergency contraceptive pill (ECP) to their local pharmacists, especially throughout the busy summer season.

Since the establishment of the 2012 Pharmacy Services Agreement, many pharmacies have provided the Community Pharmacy Anti-coagulation Management Service (CPAMS). This is a collaborative service that provides INR point-of-care testing by community pharmacy and pharmacist adjustment of warfarin doses. One of the objectives of this service is to "reduce the burden on Medical Practitioners" as well as improving the "multidisciplinary management"[5] of patients prescribed warfarin in the community. To establish this service the pharmacy must establish a collaborative relationship with their local GPs.

The success of this collaborative model of care is enabling further collaborative services to be established. We are aware of a pilot project that may soon be initiated on the West

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[4] American Pharmacists Association, 1 March 2014. *A tale of two countries: the path to pharmacist prescribing in the United Kingdom and Canada.* http://www.pharmacist.com/tale-two-countries-path-pharmacist-prescribing-united-kingdom-and-canada

[5] Interim Review of the Community Pharmacy Anticoagulation (CPAM) Service, September 2013, http://www.centraltas.co.nz/LinkClick.aspx?fileticket=PARZNNos8dk%3D&tabid=278&mid=1048

Coast using a similar collaborative model. This project would focus on the treatment of school sores and enable pharmacists to use GP standing orders to treat patients.

These examples show that collaboration is not something new for pharmacy and there is no reason to assume that pharmacist provision of OCs will not be equally collaborative.

Pharmacists are ideally placed to provide public health services such as smoking cessation, weight management and sexual health, and this aligns with intention of the new Health Minister. The Honourable Jonathan Coleman, in a presentation at the Rural Heath Conference in Rotorua on 13 March 2015 stated that he wanted "to make better use of pharmacist skills", "move health out into the community", move "services away from hospital", and use the health resources that are currently within the community. As more hospital services move to general practice it is obvious that appropriate services need to be moved further out into the community to free up doctors' time. This reclassification provides an opportunity to take some pressure off general practice and redirect some of the overflow to pharmacists who are well-placed to contribute to this changing model of care.

In a report undertaken by the Royal Pharmaceutical Society of Great Britain in November 2013[6], it was determined that "providing a proactive public health service to people coming into pharmacies" was an area where "pharmacists have the potential to help reduce demands on the NHS". The report also stated that "exercise, diet, infectious disease, drug use and sexual health are key determinants of the occurrence and severity of most of the ill health facing the NHS". The report concluded that community pharmacists should play an important role in providing these types of public health services due to the convenience of their location and availability. There is no reason to believe this would not be the same in the New Zealand environment.

A recent article by Dr Helen Roberts[7], an associate professor of women's health at the University of Auckland's Department of Obstetrics & Gynaecology, reinforces the view – that pharmacies are "well placed to improve access to services". She mentions "task-shifting", a process recommended by the World Health Organisation to transfer specific tasks to other healthcare professionals. This reclassification is an excellent example of task-shifting that has the potential to be of huge benefit to patients.

Pharmacists supplying ECP often see women who have no 'medical home'. They are often healthy young women with no other medical conditions and therefore have not considered enrolling with a general practitioner. The pharmacist-patient interaction

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6 Royal Pharmaceutical Society, November 2013. The Report of the Commission on future models of care delivered through pharmacy. Now or Never: Shaping the future for pharmacy.

7 PharmacyToday.co.nz, September 2014. *Contraception.*

provides these patients with an opportunity to talk to a health professional when they may have no other such contact.

Pharmacists triage, treat, refer as part of their every day interactions. Pharmacists help patients find their way in the health system on a regular basis.

The provision of OCs would help patients on an interim basis, by providing immediate treatment when this is appropriate. For a busy general practice, it is unlikely that a patient would be able to see a doctor on the same day for a non urgent consultation. It is more convenient for the woman to receive an initial supply of OCs from a pharmacist when she has for instance presented for an ECP consultation and thus receive a complete package of care in one place. Feedback from some of our member pharmacies indicates their frustration in providing advice to patients who are clearly using the ECP as a form of contraception, against the pharmacist's advice. For these women, this reclassification would ensure that this risky practice could be minimised with the pharmacist being able to provide ECP plus start the woman on regular contraception.

While it is widely accepted that there are current barriers to accessing health care in rural areas this can also be an issue in the cities for those women who are time-poor. Women working in the city for instance are commonly unable to access their usual GP in the suburbs at short notice. On the West Coast the Family Planning Clinic runs restricted hours, which means limited access for patients. The pharmacists in this area say that young female patients are hesitant to attempt to make urgent appointments for ECP advice at their local GP practice due to a fear of being questioned by surgery staff why they need an urgent appointment. These young women are happier with the more anonymous, walk-in service provided by the local pharmacies.

Pharmacists who have had long term experience with the supply of the ECP should be well versed to supply the OC with minimal further training. As outlined in Agenda item 6.1 our expectation would be that practicing pharmacists would ensure they are competent to provide the OC and would undertake self directed training to ensure such competence. We would support a reclassification that did not mandate additional training if that was supported by the MCC.

The reclassification of this medicine could be seen as a positive step taken by the MCC towards helping provide a solution to managing the demand on overstretched general practice services and providing the opportunity for primary care teams to work within an integrative service model.

Agenda item 7.2: Otilonium bromide – proposed classification as a restricted medicine

The Guild **supports** the proposed classification of otilonium bromide as a restricted medicine.

Irritable bowel syndrome can have a serious effect on a patient's quality of life as it can occur suddenly and at inopportune moments. Community pharmacists currently have limited ability to provide adequate treatment for these patients. There are few non-prescription medications available to patients for irritable bowel syndrome, apart from the general sales products containing peppermint oil (Mintec, Colpermin), fibre products, some probiotics and the restricted medicine Gastro-Soothe. The addition of a restricted medicine for this condition will be positive for patients who commonly present in community pharmacy requiring acute treatment.

As in our response to the reclassification of nitrofurantoin we attest that pharmacists (like GPs) are already ethically bound to learn about new medicines as they become available on the New Zealand market and to only recommend (or prescribe) a medicine they have the appropriate level of knowledge about. We refer you to the Pharmacy Council Competency Standards as listed in Agenda item 6.1.

Te Arai BioFarma Limited have stated in their submission that training material will be provided to every pharmacy in New Zealand. This will easily facilitate the upskilling required for pharmacists to deal appropriately with this newly available medicine.

The approach taken by Te Arai BioFarma Limited is similar to previous successful reclassifications from other industry submitters in terms of the package provided to pharmacy which will include a patient consultation checklist. We believe this support information is appropriate to enable pharmacists to supply this medicine should this reclassification go ahead. We support this as a standard approach for reclassifications of medicines where a health professional is required to provide oversight.

Thank you for taking the time to read our feedback. If you have any questions about our feedback, please contact our Guild Pharmacist, Professional Services and Support, Tracey Sullivan at t.sullivan@pgnz.org.nz or 04 802 8209.

Yours sincerely,

Lee Hohaia
Chief Executive