Te Kaunihera Tapuhi o Aotearoa
Nursing Council of New Zealand

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22 March 2018

Dr Stewart Jessamine
Chair
Medicines Classification Committee
PO Box 5013
Wellington 6140

Dear Dr Jessamine

Reclassification of influenza vaccine – Objection to the proposed recommendation to amend the current classification of influenza vaccine to include registered nurses

The Nursing Council was advised this month by the New Zealand Nurses Organisation (NZNO) that a proposal had been made by the Director of Public Health, Ministry of Health in November 2017 to extend the current classification to include registered nurses.

The Council understands that an objection was received on the basis that there was a breach of appropriate process. The Council would also like to endorse that there appears to be a lack of consultation and a lack of policy work before this proposal was put forward.

The Council agrees with the aim of increasing access and convenience of obtaining an influenza vaccination, in order to increase uptake by the general population and reduce the burden of influenza.

The Council agrees that the proposed reclassification would enable registered nurses with the appropriate vaccinator training to provide influenza vaccine in an agile and responsive manner.

The Council would also support a national standing order as a measure to enable this activity to take place

The Council supports the current immunisation training for registered nurses and the current mechanisms that enable registered nurses to administer vaccines as an authorised vaccinator without the need for a prescription if this is given as part of an approved immunisation programme by a medical officer of health.

The Council has introduced *Registered nurse prescribing in primary teams* with a medicines list that covers long-term and common conditions (this includes vaccines).

We are also currently trialling *Registered nurse prescribing in community health* with Counties Manukau District Health Board and Family Planning and is yet to be evaluated.

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This prescribing authority is for normally healthy patients and covers contraceptives, and antibiotics for minor infections and common ailments. Nurses have to be employed by an approved provider of a nurse prescribing recertification programme that provides clinical governance, policy, training and supervision. Vaccines were not included as nurses in general practice, public health and school nurses already have this access through standing orders or authorised vaccinator status.

The Council could consider adding the influenza vaccine to this medicines list when the trial is completed but it is not clear that this prescribing model would be relevant or available to occupational health nurses.

The Council would like to be consulted on policy changes related to registered nurse authorised vaccinators and for this to be undertaken in a planned way in consultation with nursing groups and other interested parties.

Yours sincerely

Carolyn Reed

Chief Executive/Registrar

Reclassification of Influenza Vaccine

Submission to the Medicines Classification Committee

Date: 20 March 2018

Contact

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About the New Zealand Nurses Organisation
Tōpūtanga Tapuhi Kaitiaki o Aotearoa

NZNO is the leading professional nursing association and union for nurses in Aotearoa New Zealand. NZNO represents over 49,000 nurses, midwives, students, kaimahi hauora and health workers on professional and employment related matters. NZNO is affiliated to the International Council of Nurses and the New Zealand Council of Trade Unions.

NZNO promotes and advocates for professional excellence in nursing by providing leadership, research and education to inspire and progress the profession of nursing. NZNO represents members on employment and industrial matters and negotiates collective employment agreements.

NZNO embraces te Tiriti o Waitangi and contributes to the improvement of the health status and outcomes of all peoples of Aotearoa New Zealand through influencing health, employment and social policy development enabling quality nursing care provision. NZNO's vision is *Freed to care, Proud to nurse*.

EXECUTIVE SUMMARY

1. The New Zealand Nurses Organisation Tōpūtanga Tapuhi Kaitiaki o Aotearoa (NZNO) welcomes the opportunity to comment on the proposal to extend the classification of the influenza vaccine to registered nurses (RNs).

2. We have consulted with members and staff including in particular, members of NZNO's College of Primary Health Care Nurses, the Infection Prevention and Control Nurses College, the Gerontology Nurse Section, private Occupational Health providers, and professional nursing and policy advisers.

3. We have also spoken to the Nursing Council of New Zealand (NCNZ), Ministry of Health and medical colleagues, including the New Zealand College of General Practitioners' (RNZCGP).

4. The proposed reclassification, in response to a recommendation by the Director of Public Health, Dr Caroline McElnay, is, we suggest, the wrong solution to a poorly defined problem.

5. The reclassification does little to address the equity issues with vaccination services offered by GPs, pharmacists and nurses, and poses a small risk of reducing the quality control that local vaccination programmes give.

6. In practice, we doubt it will make much difference to nurses, or improve access to affordable preventive treatment or effective utilisation of the health workforce afforded by vaccination programmes and health practitioner regulation, respectively.

7. We propose alternative solutions to current barriers to nurse-led vaccination services, with the proviso that they do not give rise to further delay in removing barriers to RN vaccinators.

8. We take this opportunity to address the concerns raised by the RNZCGP in its objection to the reclassification, which the Committee validated, particularly in relation to the lack of consultation and policy development. We agree that the processes around the proposed reclassification have been opaque and flawed.

9. We also contend that the confusion and obfuscation that continue to delay the removal of barriers to RN vaccination services in Aotearoa New Zealand, are a case study in structural discrimination that must be addressed if health outcomes are to be improved and health services sustained.

10. Although NZNO objects to, and is frustrated, by the potential for further delay in optimising safe and efficient access to influenza vaccine by removing barriers to nursing practice, we are not sanguine about the proposal.

11. The priority is the immediate removal of the anomaly of a prescription/ standing order requirement for trained nurse vaccinators to be authorised to improve access to vaccination and enable delivery models that do not discriminate against nurses.

12. It is also essential that the solution is consistent with the prescribing models NCNZ has introduced for registered nurses (RNs).

13. Because further delay could adversely affect current influenza vaccination programmes at this critical time, and continue to disadvantage nurse-led occupational health providers in particular, NZNO would support in the interim either:

    - the proposed reclassification; or

    - a Ministry of health directive to the medical officers of health to issue a standing order to enable RNs who have completed the IMAC Vaccinator Training Course to complete the clinical assessment.

14. NZNO also **recommends** that urgent attention be given to:

    - robust consultation to inform the further development of fair, consistent and well understood processes – eg common standards, portable credentialing between DHBs, equitable

access to vaccines and funded vaccines - for the safe, equitable delivery of publically and privately funded vaccination programmes, by appropriately qualified health practitioners and authorised vaccinators; and

- mitigating structural discrimination that prevents nurses working to the full extent of their scope.

DISCUSSION

Nursing and vaccination

15. Nurses comprise over half the regulated health workforce and practise in a variety of clinical contexts across Aotearoa and in partnership with individuals, families, whānau and communities.

16. Registered nurses (RNs) utilise nursing knowledge and complex nursing judgment to assess health needs and provide care, and to advise and support people to manage their health. They practise independently and in collaboration with other health professionals, perform general nursing functions, and delegate to and direct enrolled nurses, health care assistants and others. They provide comprehensive assessments to develop, implement, and evaluate an integrated plan of health care, and provide interventions that require substantial scientific and professional knowledge, skills and clinical decision making.

17. RNs are accountable for ensuring all health services they provide are consistent with their scope of practice, their education and assessed competence, meet legislative requirements, and are supported by appropriate standards[1].

18. Disease prevention and health promotion is a core component of nursing practice. Vaccination is a large part of this, and is done by RNs who are qualified, authorised vaccinators, working in a range of healthcare services including, for example, public health, primary care, occupational health, emergency, neo-natal, child health, school, Māori and iwi, Pacific, and aged care health services.

19. Nurses and pharmacists complete the same vaccinator education and training programme, through the Immunisation Advisory Centre (IMAC) to become authorised vaccinators, and to maintain competence biennially through required professional development; medical practitioners are exempt.

[1] See Registered Nurses Scope of practice, NCNZ website: http://www.nursingcouncil.org.nz/Nurses/Scopes-of-practice/Registered-nurse

Barrier to nurse vaccinators

20. Currently a prescription or a standing order is required for the two vaccinations that an RN who has completed the Vaccinator Training Course, has to do to complete the clinical assessment. The clinical assessment must be completed before the application for authorisation can be made.

21. Qualified clinical assessors who are nurses, cannot complete the assessment and authorise the vaccinator, without the prescription or standing order. Accessing either is not necessarily an issue for public health, practice nurses or pharmacists, for example, who have done vaccinator training, as there are prescribers on hand in these services. (We note however that there has been some confusion about this and the issue of inequity between nurses requiring a script and not pharmacists has recently been taken up with IMAC.)

22. It is a very real problem for nurse-led occupational health providers, however, who find it difficult to get the necessary permission. GPs are naturally reluctant to sign prescriptions for patients offered the same service by another provider, and medical officers of health, who keep the register of authorised vaccinators in their regions and who have been asked to do this, seem equally averse to issuing a standing order.

23. Prison nurses, employed by the Department of Corrections and serving a population approaching 10,000 New Zealanders have, at times, no dedicated Medical Officer available, and high turnover of medical staff means standing orders have to be constantly be updated to reflect new prescribers.

24. What appears a superficial technicality masks more serious structural discrimination both to nurses and to consumers as, in practice, there is not a level playing field between vaccination providers. Nurse-led occupational health providers have a quite different business model for delivering vaccination programmes than those based in GP practice and pharmacies.

25. Nurse-led occupational health providers focus on delivering a cost-effective vaccination service, tailored to the needs of the clients, wherever they are. ‘Flu vaccinations are usually delivered in bulk, in workplaces throughout the country, including in areas where GP and pharmacist-based services are not easily accessible, for a competitive price.

26. For employers and employees this is an innovative, cost-effective and convenient service, which encourages vaccination uptake, the public health benefits of which are well established.

27. Occupational health RNs who are authorised vaccinators, can apply for a “Local Immunisation Programme” to the relevant district health

board (DHB) to deliver immunisations in that area. The programme is valid only for two years. It requires the occupational health provider to have a Cold Chain Compliance from IMAC, and to be able to demonstrate they can provide safe immunisation. This can be a clumsy process, because each DHB has different, often inconsistent, processes and requirements.

28. There are other barriers including access to funded vaccines, and a number of petty obstructions such as limited training opportunities for non-practice based nurses as the following comment shows.

> *Each year we have experienced nurses who join our team across NZ to vaccinate in the community. They are required to do a Vaccinator Training Course with IMAC. They then are required to undergo a clinical assessment so they can apply to the relevant DHB's for Authorisation as independent vaccinators. The barriers for nurses who are not employed in General Practice are great. They are unable to access the prescription required for the vaccine that they can use for their clinical assessment. The GP's decline to issue a prescription as the vaccine is not being given in their practice. The Medical Officers of Health will not issue standing orders for the vaccines for the clinical assessments either.*
>
> *Up until this year we were only able to get our nurses places on the Vaccinator training courses if there were any spaces left after the nurses working in a GP practice had been booked. We were told they had priority over our nurses, as our nurses did not work in General Practice. Our nurses have had to travel from Auckland to towns where there were spaces left.*
>
> *Once the clinical assessments are done, then there is a time delay with the relevant Public Health services who all seem to have different processes for authorising nurses. This all causes a huge amount of stress trying to get nurses Authorised in time for the 'flu vaccinations.*
>
> *We would like to acknowledge that some progress has been made after we had a meeting with IMAC which has tried to assist with removing some of these barriers.*
>
> .**Bella Winter (NZRN)**
> **Managing Director, MEDPRO Healthcare NZ Ltd**

29. Clearly there are there are structural barriers that need to be removed to ensure an even playing field, not only between nurses and other health professionals, but also between nurses employed by different service providers.

30. Clinical and Cold Chain Assessors appear to have different standards, which powerful interests can, and often do, work to their advantage.

31. There are funding and access inequities for nurse-led services which are unable to purchase some vaccines, eg measles, even when there is an outbreak of disease and which don't have access to funded vaccines, including influenza vaccine. For example influenza vaccine is funded for people over 65, but while GPs and pharmacists vaccinating people over 65 can apply for a refund, nurses cannot.

32. Regulation should support a level playing field for all approved providers, enhance continuity and efficiency, and ensure that the same standards apply to all.

33. Authorisation also needs to be portable between DHBs, to unnecessary duplication with vaccinators having to go through a superfluous, and for experienced vaccinators, demeaning process of authorisation for each DHB.

34. Any unnecessary impediment to the efficient delivery of literally tens of thousands of influenza vaccinations will have adverse consequences for providers and consumers, and will not be cost effective or deliver optimal public health benefits.

Potential risks of the proposed reclassification

35. The Local Immunisation Programme requirement would be removed with reclassification of the influenza vaccine.

36. That raises important questions about the monitoring and quality assurance of vaccination. Expert nurse vaccinators are wholly supportive of the local immunisation programmes as they offer the flexibility of being able to respond promptly and efficiently to local outbreaks, and the security provided by careful monitoring.

37. Removing the Local Immunisation Programme requirement would remove a safety and quality assurance check that has proved useful.

38. With increased infection risks from global travel, trade and migration, and the impact of climate change, it seems prudent to keep such protections.

Alternative solutions

39. Reclassification of the influenza vaccine was proposed as a quick solution to avoid a potential shortage of vaccinators, as the 2018 'flu vaccination programme starting in March would need to be delivered at the same time as the zoster vaccine programme.

40. There is still the need for an immediate solution, but preferably not one that would undermine due process or risk adverse

consequences such as lowered quality assurance, or the introduction of a different process for authorising nurse prescribing of particular medications.

41. It is essential that the solution is consistent with the prescribing models NCNZ has introduced for registered nurses (RNs).

42. The current process for authorising nurse prescribing is that it is gazetted by NCNZ, after robust and comprehensive consultation.

43. Nurses who have done an additional qualification, a post graduate diploma, are authorised to prescribe in primary health and specialty teams and can prescribe vaccines. However this qualification is unnecessary for most nurses delivering vaccinations, including occupational health nurses.

44. In relation to influenza vaccine, the competence and safety parameters, namely completion of the IMAC Vaccinator Training Course, have already been established for nurses – as well as pharmacists. IMAC is contracted by the Ministry of Health to provide the required programmes and ongoing professional development nationally and there is no need to duplicate what has proven to be a robust and effective system.

45. Consideration could be given to including influenza vaccine in the community health prescribing model for nurses which is currently being trialled at Counties Manukau DHB; however, this will take time and would not address the issues that occupational health nurses face.

46. Clearly there needs to be better understanding of how vaccination programmes and services are delivered to accurately identify the barriers to RNs, and robust consultation to arrive at a practical solution that is fair and efficient.

47. NZNO's main concern is that abandoning reclassification at this stage may mean further delay in removing the technical barrier that impedes occupational health nurses who have completed the vaccinator training course, completing the clinical assessment enabling them to be authorised.

48. That would be an extremely unfortunate outcome, since it could be perceived that NZNO, in acting in the best interests of health and rational policy, could be seen to have prevented the removal of this barrier. It would not be the first time that nurses have been put in such a 'catch-22' situation where they appear divided or one nursing group has been held responsible for obstructing the removal of barriers to nursing practice.

49. If further delay were to be the case, as is likely, NZNO would, in the interim, support either*:*

- the current proposal; or
- a Ministry directive to the medical officers of health to issue a standing order for to enable RNs who have completed the IMAC Vaccinator Training Course to complete the clinical assessment.

50. Another suggested solution would be to consider simulation. This would enable completion of the clinical assessment by RNs who know how to insert a needle into a real person, so that the authorisation process would not be held up.

51. In addition to solving this particular issue, NZNO strongly recommends that DHBs develop standard processes and a more integrated and collaborative approach to immunisation.

RNZCGP

52. Notwithstanding our disappointment with the delay in acting on the proposal, which was itself late in coming, NZNO agrees with the concerns raised by the RNZCGP that the consultation process was flawed.

53. Key stakeholders – for example, the New Zealand Occupational Health Nurses Association and NCNZ - were unaware of both the original proposal and this consultation until NZNO alerted them as part of our own consultation processes.

54. That is unacceptable. Robust consultation is an integral part of sound policy development, decision making and implementation and reduces the risk of unintended adverse consequences.

55. We recommend to your attention to the recommended guidelines for consultation in:

    - Section 7 of the Local Government Act which stipulates a minimum of four weeks and a maximum of three months;
    - the Ministry of Health consultation guidelines for District Health Boards relating to the provision of health and disability services (2002)[2]; and

[2] http://www.moh.govt.nz/notebook/nbbooks.nsf/0/7DA9155B78CF5A05CC257A990002EE58/$file/consultation-guidelines-links.pdf

- the Cabinet Manual[3] which advises that "Effective and appropriate consultation is a key factor in good decision making, good policy, and good legislation" and requires "realistic time frames".[4]

56. Although the Committee's work is transparent in that it is published online, members generally find it difficult to access the information they need and unless specifically alerted, are generally unaware of consultations.

57. We suggest that the Committee has a responsibility to both inform and consult with its stakeholders and we respectfully suggest that a more proactive approach is needed than relying on the website and/or publishing meeting minutes.

58. Other agencies for instance, email stakeholders directly and post consultations on their websites.

59. The RNZCGP also noted the processes followed when pharmacist vaccination was introduced a few years ago, and asked if the same were being considered for nursing – evidence enough, we suggest, of the lack of information and understanding of standard processes for authorising vaccinators, confusion around some aspects of cold chain supply and comprehension of the rigorous processes and regulations nurses have to comply with to be able to vaccinate like other health professionals.

60. Nurses have been the key delivery agents of public health vaccination programmes for decades and while, in one sense, it is perhaps understandable that pharmacists should develop their own processes for a new areas of practice, it is mystifying why the opportunity was not taken at the time to ensure consistency for all regulated health practitioners, particularly experienced nurse vaccinators.

61. The RNZCGP noted that the Pharmaceutical Society maintains a register of authorised vaccinators. NZNO is the equivalent professional body for nurses, and we do not think it in any way appropriate, or the responsibility of a member organisation, to keep such a register.

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[3] https://www.dpmc.govt.nz/our-business-units/cabinet-office/supporting-work-cabinet/cabinet-manual

[4] You may also be interest in the following article by Lyndon Keene. Consultation or 'Public relations', *The Specialist* 2016 March. P8. , ASMS. Retrieved March 2017. http://www.asms.org.nz/wp-content/uploads/2016/03/10985-The-Specialist-Mar16-WEB-1.pdf

Structural discrimination

62. Finally we take this opportunity to point out that this delayed and mismanaged response to a workforce barrier is symptomatic of the glacial progress in recognising the education and training underpinning 21st century nursing scope or practice and removing (one by one) barriers to integrated nursing practice.

63. It contrasts sharply with the speed with which in the past few years, other scopes of practice have been introduced and expanded, including in relation to prescribing and vaccination.

64. Nursing is overwhelmingly a female-dominated profession, and, as well as gender bias, still contends with the outdated, hierarchical workforce and healthcare models which embed structural discrimination and are a barrier to equity and integrated multidisciplinary care (Human Rights Commission, 2012).

65. The protracted process for recognising and appropriately addressing both the technical and commercial barriers to nurse-led vaccination services is a case in point. Despite numerous approaches to government authorities, a succession of policy papers and promises, a long history of nurse vaccination, and regulatory potential, the reality is that RNs face barriers to their practice that other health practitioners do not and that innovative, nurse-led businesses face a 'closed shop' as both traditional GP and new pharmacy-based funding models exclude nurses.

66. Equitable, cost-effective access to 'flu vaccine largely depends authorised RNs being able to deliver it to *all* consumers in a timely and convenient way, including in settings where there is no GP practice and no pharmacy.

67. Nurses in all areas are disadvantaged by the hoops they are required to jump through, and the consequences are not confined to them as individuals, but systemically affect the efficiency of public health services and those to whom they are delivered.

68. Those most disadvantaged by barriers to nurses delivering occupational health vaccination programmes, eg in areas where there low density, poor access to primary care, poor health literacy, lack of transport, cost and cultural issues etc. are often those from vulnerable population groups, who stand to benefit the most from vaccination, eg low income, rural, Māori, Pacific peoples, refugees.

CONCLUSION

69. Having spent considerable time over the past few weeks unravelling the layers of inconsistent, confusing and disparately understood

information pertinent to the proposed reclassification, NZNO is convinced that it is the wrong solution to a poorly defined problem.

70. Implementing risks unintended adverse consequences, yet further delay simply impedes the fair, efficient delivery of vaccination programmes – we should not lose sight of the fact that vaccination is one of the most effective means of improving population health and equity.

71. It is also essential that the solution is consistent with the prescribing models NCNZ has introduced for registered nurses (RNs).

72. Because further delay could adversely affect current influenza vaccination programmes at this critical time, and continue to disadvantage nurse-led occupational health providers in particular, **NZNO would support in the interim** either:

    - the proposed reclassification; or
    - a Ministry of health directive to the medical officers of health to issue a standing order to enable RNs who have completed the IMAC Vaccinator Training Course to complete the clinical assessment.

73. NZNO also **recommends** that urgent attention be given to:

    - robust consultation to inform the further development of fair, consistent and well understood processes – eg common standards, portable credentialing between DHBs, equitable access to vaccines, and funded vaccines - for the safe, equitable delivery of publically and privately funded vaccination programmes, by appropriately qualified health practitioners and authorised vaccinators; and
    - mitigating structural discrimination that prevents nurses working to the full extent of their scope.

74. NZNO would be happy to discuss any of the above.

Marilyn Head

Senior Policy Analyst

REFERENCES

Human Rights Commission. (2012). *Addressing Structural Discrimination in Public Services A fair go for all ?* Wellington.

PHARMACY GUILD OF NEW ZEALAND

22 March 2018

Medicines Classification Committee Secretary
Medsafe
Wellington

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

Dear Sir/Madam

RE: AGENDA FOR THE 60th MEETING OF THE MEDICINES CLASSIFICATION COMMITTEE

Thank you for the opportunity to provide feedback on the agenda for the 60th meeting of the Medicines Classification Committee (MCC), to be held on Thursday 26 April 2018.

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 5.3: Trimethoprim – usage and resistance following reclassification
- Agenda item 6.1: Clotrimazole and hydrocortisone - proposed reclassification from restricted medicine to pharmacy-only medicine (Canesten Plus, Bayer New Zealand Limited)
- Agenda item 6.2: Loratadine – proposed reclassification from pharmacy-only medicine to general sale medicine (Claratyne, Bayer New Zealand Limited)
- Agenda item 6.3: Influenza vaccine – proposed amendment to prescription except when classification (Pharmaceutical Society of New Zealand)
- Agenda item 6.4: Melatonin – proposed reclassification from prescription medicine (Individual submission)
- Agenda item 6.5: Modified-release paracetamol – proposed reclassification from pharmacy-only medicine to restricted medicine.
- Agenda item 6.6: Sedating antihistamine – proposed amendment to restricted medicine classification

Each of these agenda items are discussed below.

Agenda item 5.3: Trimethoprim – usage and resistance following reclassification

The Guild **supports** Medsafe's decision that a review of the reclassification is not required at the current time. From the available information, there is no evidence that the introduction of trimethoprim supplied by pharmacists has had an impact on the incidence of resistance to trimethoprim. Since the reclassification, the increase in rate of resistance to trimethoprim in New Zealand is less than in Australia, where it is classified as a prescription medicine.

The data collected from PHARMAC does not include the amount of trimethoprim supplied by pharmacists because the data is not available. The data collected by ESR does not differentiate between providers and is only for *Escherichia coli* isolated from urinary samples. Currently ESR does not collect trimethoprim resistance data for any other urinary pathogen. Therefore the data does not contribute to any meaningful analysis to determine the impact that pharmacists supply has on the overall resistance to trimethoprim in New Zealand.

Agenda item 6.1: Clotrimazole and hydrocortisone - proposed reclassification from restricted medicine to pharmacy-only medicine (Canesten Plus, Bayer New Zealand Limited)

The Guild **opposes** the proposal to reclassify clotrimazole and hydrocortisone from restricted medicine to pharmacy-only medicine. This company submission from Bayer New Zealand Limited is seeking the reclassification of their proprietary product Canesten Plus topical cream which contains clotrimazole 10mg/g and hydrocortisone 10mg/g (as acetate).

Clotrimazole topical cream at this strength (10mg/g) is currently a pharmacy-only medicine, therefore this submission is seeking the reclassification of hydrocortisone 10mg/g (1%) for dermal use when combined with an antifungal substance. The Guild believes that hydrocortisone 1% topical preparations, with or without an antifungal, should remain a restricted medicine.

Community pharmacists regularly have to explain hydrocortisone's purpose to patients. Pharmacists need to tell patients that hydrocortisone is not an antifungal agent, but is used to reduce inflammation and itching, and should only be for short-term use unless under the treatment of a doctor. However, the actual antifungal treatment needs to be continued for two weeks after the infection has cleared. It needs to be explained to the patient that there are no benefits and some risks from prolonged use of a steroid.

We are concerned that long-term steroid use will mask the symptoms of an infection when it is not improving. Pharmacists are wary of hydrocortisone being used inappropriately on other skin lesions like cold sores. Our members are also concerned that if this reclassification goes ahead patients will soon learn that hydrocortisone 1% is available in a combination form without pharmacist consultation and will purchase this to treat dermatitis even when an antifungal is not warranted.

For the reasons discussed above the Guild is also concerned about the impact on patient safety as the company currently has another proprietary product approved for distribution in New Zealand, Canesten Extra topical cream, which contains exactly the same formulation as Canesten Plus topical cream. Canesten Extra is classified as a restricted medicine and the company is retaining this as a pharmacist-only option. This will result in inconsistencies about appropriate indications for the use of hydrocortisone 1% and be a source of confusion for consumers and frustration for pharmacy to manage consumer expectations, despite the use of required labelling indications and warnings.

Agenda item 6.2: Loratadine – proposed reclassification from pharmacy-only medicine to general sale medicine (Claratyne, Bayer New Zealand Limited)

The Guild **opposes** the Bayer New Zealand Limited company submission proposing an amendment to the Label Statements Database to change the general sales restriction on age from 12 years and older to six years and older for loratadine.

We believe that changing the general sales restriction on age from 12 years and older to six years and older for loratadine will send a message to the public that this medicine can be taken by everyone, without risk. Loratadine interacts with a small number of medicines, namely antibiotics. Antibiotics are often prescribed for children six years and older and the provision of professional health care advice does not fall within the responsibility of general sellers, such as supermarkets, or the competency of their staff.

The proposal to amend the Label Statements Database for loratadine underestimates the value of the important role that community pharmacy plays in ensuring medicine safety for children aged under 12 years in the primary care setting. Pharmacy-only medicines when supplied have the oversight of pharmacists who have significant clinical expertise and where needed, patients can be provided with medicines information, advice and verbal reinforcement.

We are concerned changing the general sales restriction on age for loratadine encourages the public to self-diagnose for children aged under 12 years for a condition that is often misdiagnosed by the public. Seasonal allergic rhinitis is commonly confused with a range of other diagnoses, such as a simple cold, a sinus infection, conjunctivitis, and serious eye conditions. Due to the prevalence of misdiagnosis, there is potential risk to deterioration of the child's health due to inappropriate treatment. When purchasing loratadine for children aged under 12 years the public should have access to health care advice to determine whether it is the most appropriate treatment for their child's condition. In some cases, a child may need to be referred to another health provider for further diagnosis to achieve the best outcome.

The Guild is somewhat reassured to note Bayer proposes that the unscheduled product not be used for first-time sufferers unless there is a health care professional diagnosis of seasonal allergic rhinitis. Therefore, a safety statement 'Do not use this product when experiencing first-time hay fever symptoms without advice from a healthcare professional' is proposed to be included on the product labelling. However, for the public to be aware of this warning before purchasing as a general sale item, this safety statement would need to be in bold lettering on the outside of the packaging.

Agenda item: 6.3 Influenza vaccine – proposed amendment to prescription except when classification (Pharmaceutical Society of New Zealand)

The Guild **supports** the proposed amendment to the 'prescription except when' classification of influenza vaccine to include registered intern pharmacists who have successfully completed a vaccinator training course approved by the Ministry of Health and who comply with the immunisation standards of the Ministry of Health.

The EVOLVE intern training programme provides practical training and support for Bachelor of Pharmacy graduates in their final stage of becoming qualified pharmacists.

The purpose of the programme is to produce pharmacists who are workforce ready at completion of the programme.

The intention of the proposal is to allow interns to become trained vaccinators and have clinical experience during their intern year so they are ready to provide vaccinations as soon as they become a registered pharmacist. This will allow for influenza vaccination to become a central part of a pharmacist scope of practice.

Pharmacists have been providing vaccinations since 2012 and in that time the profession has received training through a recognised and established programme. Community pharmacy currently provides funded influenza vaccinations to those who meet the PHARMAC eligibility criteria for pharmacy services which includes pregnant women (any trimester) and people aged 65 years or older.

The Immunisation Advisory Centre has set goals for 2018 to vaccinate 75% of the population aged 65 years or older against influenza annually, improve the influenza immunisation coverage for people aged under 65 years with certain medical conditions, and pregnant women, and to distribute more than 1.2 million influenza vaccine doses annually (ie, protect more than 25% of the community)

Pharmacists are well positioned in the community to help increase vaccination targets through their accessibility to the patients and the convenience of providing vaccinations without an appointment. By allowing for intern pharmacists to become vaccinators this will have a direct benefit to making the service more accessible and available to patients.

This proposal will align the intern scope of practice with the Pharmacy Action Plan. The Action Plan sets the intention to provide high-quality pharmacist services in an evolving health care environment. It emphasises the importance of taking a clear and combined approach so that the role of pharmacy in the health care model becomes reality. This proposal means that on completion of the intern training programme, qualified pharmacists can more readily contribute to providing better health outcomes to the general population of New Zealand.

Agenda item: 6.4 Melatonin – proposed reclassification from prescription medicine (Individual submission)

The Guild **supports** the proposal for oral melatonin to be allowed to be purchased under the instruction of a pharmacist. However, we **oppose** the proposal for oral melatonin in doses of 3mg or less to be classified as a dietary supplement and the proposal to instruct Medsafe to allow the mail order of up to three months supply of 3mg tablets for personal use from countries where it is legal to purchase as a dietary supplement.

Melatonin holds various classifications in a number of international jurisdictions, however in New Zealand it is currently classified as a prescription medicine. A more appropriate classification would be to declassify the medicine to a restricted (pharmacist-only) medicine.

It has been proposed previously on several occasions to change the classification to pharmacist-only. At previous meetings it has been established that the safety and

efficacy profiles of melatonin are better than current treatment options that are available for pharmacists to recommend. Melatonin has been marketed in New Zealand as Circadin for over ten years so extensive safety and efficacy data should be sufficient to meet the committee's criteria to change to a non-prescription medicine.

At the 16th meeting of the medicines classification committee in 1996, melatonin was changed to be classified as a prescription medicine as there was insufficient data available regarding its effects and safety profile. However, at subsequent meetings in 2012, the committee established that melatonin had an acceptable safety profile and had sufficient evidence of efficacy to support. It has also been shown that melatonin does not induce tolerance over time and that patients do not suffer withdrawal effects. The committee has also agreed that the short-term side effect profile of melatonin may be considered safer than those sedating antihistamines which are restricted medicines used to treat insomnia.

Melatonin has been approved for use in insomnia for short-term use for adults over 55 years for up to 13 weeks. Therefore, we would support applying this same indication when sold by a pharmacist.

We feel the discussion to reclassify melatonin to pharmacist-only should be looked at again to determine what currently needs to be addressed to ensure melatonin is suitable to be reclassified to pharmacist-only.

Agenda item: 6.5 Modified-release paracetamol – proposed reclassification from pharmacy-only medicine to restricted medicine.

The Guild **supports** proposing the reclassification of modified-release paracetamol from pharmacy-only medicine to restricted medicine.

Paracetamol is the most commonly used pain relief medicine in New Zealand. Used at the appropriate doses for the patient, it is a very safe medication. However, when used incorrectly it can have significant complications.

The concerns around the proposal lie in the different dosing profile of modified-release paracetamol compared to the immediate-release formulation, and the ability to manage paracetamol toxicity using current treatment protocols.

Modified release paracetamol usage is relatively small in comparison to the more familiar immediate-release formulation. Consequently, there is a clear misunderstanding as to the difference between the products. From the National Poisons Information Centre data, therapeutic dosing error comprised of three quarters of the calls received around modified-release paracetamol.

We believe the change in classification to a restricted medicine will take measures to resolving the current dosing errors. When medicines are classified as pharmacist-only medicines, this requires that each sale to a patient will be individually checked by a pharmacist. Pharmacist are the guardians of safe medication usage and this will ensure that when patients require any medication, the suitability of a medicine will always be assessed.

Through the consultation, the need for a particular treatment is assessed and then the patient is given individualised information and advice to suit. Part of that information will be to clearly explain the difference between modified-release paracetamol and immediate-release paracetamol. Changing to pharmacist-only will remove the opportunity for impulse purchasing, or unintentionally purchasing the wrong product, and this will also avoid accidental overdoses which can occur when modified-release paracetamol is mixed with other medication containing paracetamol.

Agenda item: 6.6 Sedating antihistamine – proposed amendment to restricted medicine classification

The Guild **supports** the proposed amendment to remove 'for the treatment of anxiety' from the restricted medicine classification statements.

We are supportive of the proposed amendment as it will not have any change to current pharmacy practice and it will help to avoid any confusion to the patient that might exist from the current classification statements.

Best practice guidelines do not include sedating antihistamines as a recommended treatment for Generalised Anxiety Disorder. The only antihistamine that carries the indication for treatment in anxiety is hydroxyzine, but this medicine is not available in New Zealand. In pharmacy practice sedating antihistamines are only recommended for the treatment of allergies, short-term insomnia, motion sickness and when used in cold and flu preparations.

Thank you for your consideration of our response. If you have any questions about our feedback, please contact our Professional Services Pharmacists, Alastair Shum, at a.shum@pgnz.org.nz ph: 04 802 8209 or Linda Joe, at l.joe@pgnz.org.nz ph: 04 802 8214.

Yours sincerely,

Nicole Rickman
General Manager – Membership and Professional Services

The Royal New Zealand
College of General Practitioners
Te Whare Tohu Rata o Aotearoa

22 March 2018 Our ref: MT18-380

Jessica Lo
Advisor Science (Secretariat - MAAC and MCC)
Medsafe
Ministry of Health
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Email committees@moh.govt.nz

Dear Jessica

Thank you for the opportunity to comment on the agenda of the 59th meeting of the Medicines Classification Committee (MCC) of Medsafe.

RNZCGP Comments on the agenda of the 60th meeting of the Medicines Classification Committee

Introduction to general practice and the College

General practice is the medical 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 GPs and rural hospital generalists, and sets standards for general practice. The College has a commitment to embed the three principles (participation, partnership and protection) of Te Tiriti o Waitangi (Treaty of Waitangi) across its work, and to achieving health equity in New Zealand.

Health equity is the absence of avoidable or remediable differences in health outcomes and access to health services among groups of people, whether those groups are defined socially, economically, demographically, or geographically (WHO). To achieve health equity, we advocate for:

- A greater focus on the social determinants of health (including labour, welfare, education, housing, and the environment).
- Funding and support to sustain the development of a GP workforce of sufficient capacity to meet population need for access to quality primary medical care, particularly in rural and high need areas.
- Sustained focus on measures to reduce smoking and to increase healthy food options for low-income families.
- Improved integration of primary, community, and secondary care health and social services which ensures the provision of high quality services.
- Universally accessible free primary health care for children and low-income families, because health inequities begin early and compound over the life course.
- A review of the funding model for primary care to ensure that resourcing is allocated equitably across diverse populations with differing needs.

Submission

The College would like to comment briefly on each of the following agenda items

5.5 Phenibut

5.6 Rilmazafone

6.1 Canesten plus

6.2 Loratadine

6.3 Influenza vaccine

6.4 Melatonin

6.5 Modified release Paracetamol

6.6 Sedating antihistamines

Items 5.5 and 5.6 Phenibut and Rilmazafone

The College supports the proposals to classify Phenibut and Rilmazafone as prescription medicines. A prescription only status for these medications would close a loophole under which importers can claim they are importing these substances into New Zealand for personal therapeutic use. These substances can already be stopped at the border under the Psychoactive Substances Act 2013 but only when imported for the purpose of inducing a psychoactive effect. By claiming that the product is instead being used for personal therapeutic use importers can bypass the provisions of the Act.

As stated in the attachment to the Medsafe Submission relating to Phenibut "The medical conditions phenibut is reportedly being used to treat (including anxiety and sleep disorders) are better managed by a medical practitioner".

Item 6.1 Canesten plus

The College opposes the reclassification of Canesten plus from Restricted (pharmacist only) to pharmacy only. Canesten plus contains Hydrocortisone 1%. At this strength Hydrocortisone is a restricted medicine.

Reclassification would allow Canesten plus to be stocked on the open shelves of the pharmacy, self-selected by customers and sold by any pharmacy staff member, thus by passing the opportunity for health practitioner advice. There is potential for repeated use for short term relief of conditions that could or should be treated with more appropriate medications. The College considers that it is important that the pharmacist has the opportunity to give advice on more appropriate medication or management.

Item 6.2 Loratadine

The College supports the proposal to lower the age at which loratadine is available to children under general sale from 12 years to 6 years.

6.3 Influenza vaccine

The College supports the proposal to allow pharmacy interns with approved training to administer influenza vaccination under the direct supervision of a trained pharmacist vaccinator.

Item 6.4 Melatonin

There was support from some College members for increased accessibility of Melatonin. However we note that dietary supplements "cannot have a stated or implied therapeutic purpose".[1] Hence such a classification may not be appropriate.

[1] http://www.medsafe.govt.nz/regulatory/DietarySupplements/Regulation.asp accessed 22/3/18

Item 6.5 Modified-release Paracetamol

The College supports the Medsafe proposal that modified release paracetamol be reclassified from a pharmacy-only medicine to a restricted medicine. With the many forms of paracetamol available on pharmacy shelves it is not surprising that the higher dosage of modified-release Paracetamol is sometimes overlooked. Poisons Centre data showing that 77% of calls relating to modified-release paracetamol concern therapeutic error, compared to only 22% of calls regarding all paracetamol, provides evidence of this. By requiring contact with a pharmacist for the purchase modified-release paracetamol there will be the opportunity to ensure that the patient is aware of the higher dose and that the medication is used appropriately.

Item 6.6 Sedating antihistamines

The College agrees that anxiety is not an appropriate indication for the use of sedating antihistamines. Removing this indication for the label statement database will prevent patients from being misinformed, and discourage this inappropriate use.

We hope you find our submission helpful. Should you require any further information or clarification please contact the College's policy team at policy@rnzcgp.org.nz.

Yours sincerely,

Michael Thorn
Manager – Strategic Policy

26th March 2018

The Medicines Classification Committee Secretariat
Medsafe
PO Box 5013
Wellington

Dear Committee Members,

Re: Agenda for the 60th meeting of the MCC, item 6.4, melatonin

Thank you for the opportunity to comment on the proposed reclassification of melatonin. The proposal suggests supplement status.

In New Zealand, there is one registered medicine for melatonin, and this is Circadin®, 2 mg prolonged release melatonin. Its licensed indication is "Monotherapy for the short term treatment of primary insomnia characterized by poor quality of sleep in patients who are aged 55 or over", and treatment is limited to 13 weeks.(1)

Exemption of melatonin 2 mg prolonged release to prescription status through specially trained pharmacists

We would support an exemption to prescription status through specially trained pharmacists of New Zealand-registered prolonged release melatonin 2 mg for the licensed indication of primary insomnia in adults 55 years and over. This is currently the only licensed melatonin formulation available in New Zealand, that has been confirmed of pharmaceutical quality (through regulatory licensure) and has proven efficacy sufficient to satisfy regulators.

Such availability would also allow triage to doctors of people where the pharmacist identifies a need for referral.

An exemption to prescription status for trained* pharmacists provides an opportunity for an evidence-based treatment and formal screening process. This maximises quality use of medicines, and, as an additional benefit, would likely see people with underlying concerns such as possible depression, anxiety disorders or sleep apnoea being referred to doctors for early assessment without treatment from the pharmacy.

**We envisage this would be via the provision of a screening tool for pharmacists and information sheet for consumers that has already been prepared by Dr Natalie Gauld, the leading expert in New Zealand for preparing materials for reclassifications, with input for a sleep specialist, general practitioners, pharmacists and medical and pharmacy organisations. Development and consultations has already been undertaken on such a tool.*

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We do not recommend the availability as a supplement for several reasons which we have outlined below. We note the 2016 recommendation by the Advisory Committee for Medicine Scheduling (ACMS) in Australia (reported 23 March 2017)(2) that supplement status for a 1 mg product was not appropriate. Concerns highlighted included indiscriminate use/misuse by consumers, and potential for underlying sleep conditions not being diagnosed or managed properly, especially in children. This recommendation was followed by the Delegate for the Secretary for the Department of Health who confirmed the current scheduling remained appropriate.

We also do not recommend availability through mail order from overseas. There is a registered medicine in New Zealand that can be dispensed pursuant to a prescription (with medical diagnosis and oversight), or could be available through specially trained pharmacists (where indicated, and with medical referral in other cases) if the above reclassification suggestion is followed. There is no need for a less safe availability of unrestricted supplements.

Use in Children

The greatest concern for the proposed reclassification as a supplement is that parents will use melatonin first-line in children without any medical consultation, recommendation or oversight. Insomnia is a common complaint in childhood (occurring in 20-30% of children and adolescents) and requires comprehensive assessment and health professional diagnosis.(3) The most common cause of insomnia in children is Behavioural Insomnias of Childhood, probably caused by problems with parents failing to set clear limits for sleep or sleep training issues.(4) Poor parental management of bedtime stalling, for example, can delay sleep onset. (4) Children can become dependent on specific objects or settings to get to sleep or return to sleep if they awaken, such as the parent being present for them to fall sleep.(3)

An expectation will be likely amongst consumers that melatonin is safe long-term for them and their children if it is readily accessible in supermarkets and health food stores. We anticipate it is likely that such supplements would be promoted to consumers to “support sleep”, leading to wide use of the product, particularly in children, and without medical management or implementation of the recommended sleep hygiene and other behavioural measures. This is inconsistent with best practice recommendations for sleep in children, and will create more problems than it will solve.

Widening availability of melatonin without a health professional being involved, such as a doctor is likely to see parents routinely dosing children with melatonin to get them off to sleep. Indeed the five-fold growth in melatonin use in children in the US from 2007-2012 that saw an estimated 419,000 children aged 4-17 years old using it in 2012 is evidence of such behaviour.(5) This made it the second most commonly used complementary remedy used in US children. Increasing developments in sleep aids in the US are of liquids and forms that dissolve in the mouth (“melt-aways”). Such formulations would be likely to help administration in children. A supplements consultancy business noted that “children and sleep is a very large Level 2 mass market … and is virtually untapped by major marketers beyond kids’ homeopathic options”.(6)

Pharmaceutical Grade Quality

Melatonin has pharmacological activity, and it is important to have confidence in the quality used. This is even more important when it is likely to be used in children on a long-term basis without medical oversight if unregulated supplement-status occurs.

Considerable variability in contents and quality concerns, including contamination with undeclared active substances and arsenic, of unregistered melatonin supplements has been found in developed markets.(7-10) Regarding availability of melatonin in the UK, the National Health Service states:(11)

> *"…many unlicensed products are imported from the USA where they are classified as supplements, and are not licensed as medicines. As a result, quality and consistency is not guaranteed. According to the MHRA's [Medicines and Healthcare Products Regulatory Agency] risk hierarchy, these USA-made imported products should only be used as a last resort."*

Multiple batches of an unregistered melatonin (supplied under Section 29 of the Medicines Act) were recalled in August 2016 in New Zealand owing to contamination.

Pharmacovigilance data is collected and reported for prescription medicines, which is not the case for dietary supplements.

Insomnia in adults – underlying conditions and best practice

The probable purposes for use need consideration. Insomnia is a common complaint, and has a number of possible underlying factors, with a minority of cases of insomnia not having secondary causes.(12) These factors include anxiety, depression, sleep apnoea, certain chronic conditions, and parasomnias. It is important that a healthcare professional is involved in management of such conditions. For example, an estimated 40% of people suffering from insomnia have a coexisting psychiatric condition.(13) With melatonin as a supplement, self-selection and self-diagnosis would occur without any health professional involvement. On the other hand, we recommend availability through specially trained pharmacists using carefully developed screening tools, triaging to the doctor as appropriate, discussing sleep hygiene as a first-line management strategy, then providing written and verbal information to the patient when it is supplied and limiting supply to 13 weeks.

Other uses of melatonin

A quick scan of the internet finds that melatonin is purported to have anti-cancer effects, boost the immune system, help menopause, depression, fibromyalgia, migraine, epilepsy, "growing muscle" and irritable bowel syndrome. Robust evidence is generally lacking and melatonin has not been adopted into mainstream medicine for any of these conditions. Furthermore, medical management is necessary for most of these conditions, but there is a likelihood of uptake by consumers without consulting a doctor with an unscheduled melatonin readily available.

Other safety concerns

The product information for the licensed 2 mg prolonged release product in New Zealand recommends avoidance of the product in pregnancy or by women intending to become pregnant; women who are breast-feeding; people with auto-immune disorders, and use with fluvoxamine (which can increase bioavailability by 17-fold).(1) Other interactions are also listed.

Conclusion

We would support a reclassification to prescription except when supplied through specially trained pharmacists. This would be consistent with the safety of the medicine. This would provide an appropriate level of access to this proven medicine and result in medical referrals of patients who may have concerning conditions underlying their insomnia, as well as sleep hygiene advice.

Yours sincerely,

[redacted]

[redacted]

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22nd March 2018

The Secretariat
Medicines Classification Committee
Medsafe
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Wellington

Dear Jessica,

Re: Medicines Classification Committee 60th meeting, 26 April 2018.
Thank you for the opportunity to comment on the agenda items for the upcoming 60th MCC meeting.

Item 5.1.1 Reclassification of influenza vaccine
We consider and are supportive of nurses who have successfully completed the MoH approved vaccinator training and two-yearly updates to be capable of administering the Influenza vaccine without requiring standing orders, providing similar safety measures are in place as have occurred for pharmacy. This was noted to be aligned with the pharmacist vaccinator reclassification, so we would recommend, that, like the pharmacist vaccinator status, appropriate screening tools are made available to nurses, as we have done in pharmacy, and that the GP is notified with patient consent (where it is done outside of a GP practice). We understand that cold chain accreditation will be part of the vaccinator authority. Furthermore, we would assume that auditing of nurses would occur as for pharmacy, to check appropriate Standard Operating Procedures and requirements are in place, including for adverse reaction management and reporting, and that supply is in line with the screening tool. As for pharmacy, presumably the Nurses Organisation will maintain an up-to-date list of nurses qualified to do vaccination.
We would welcome similar submissions from the Director of Public Health for pharmacists to provide other vaccines without a prescription to benefit the health of all New Zealanders.

Item 5.3 trimethoprim
We are pleased to see the paper on the reclassification of trimethoprim and resistance. Minimising the opportunity for resistance has been a priority in how this reclassification was planned and managed from the beginning. The paper helpfully provides data over a nine-year period for supplies and resistance.
Resistance needs to be considered and so does changing usage over time. We note the point made "that to monitor the change of classification of trimethoprim in a robust manner, monitoring the use of a range of antibiotics across all prescribers as well as the rates of resistance of bacteria associated with urinary tract infection would be required". To this end Green Cross Health (and others in the NZ pharmacy sector) supported research conducted in 2012 and 2013, before and after the reclassification. We refer the committee to the attached research references and will discuss usage below.

Gauld NJ, Zeng ISL, Ikram RB, Thomas MG, Buetow SA. Antibiotic treatment of women with uncomplicated cystitis before and after allowing pharmacist-supply of trimethoprim. *Int J Clin Pharm.* 2017;39(1):165-172.
Gauld NJ, Zeng ISL, Ikram RB, Thomas MG, Buetow SA. Treatment of uncomplicated cystitis: analysis of prescribing in New Zealand. *NZ Med J.* 2016;129(1437):55-63.

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To reduce the risk of resistance of bacteria, it is recommended that compliance with local guidelines in drug, dose and duration occurs.(1) The research by Gauld, et al,(2, 3) conducted in 2012 (pre-reclassification) and one year after reclassification in late 2013 reported prescribing in cystitis by New Zealand prescribers. The research reveals that guideline compliance of prescriptions for women with cystitis without complicating features was 72.2% for the chosen drug, and 20.6% in terms of drug, dose and duration. The use of funded norfloxacin later reduced after Pharmac changed the funding criteria.(2)

Guideline compliance in pharmacist-supply under strict criteria is ensured by using a screening tool under which supply is limited to typical symptoms of cystitis with no complicating features in women aged 16 to 65 years, and supply can only be trimethoprim 300 mg once daily for three days, a drug, dose and duration consistent with the guidelines for antibiotic used published by the Best Practice Advocacy Centre (BPAC). The latest guidelines (2017) have nitrofurantoin 50 mg four times daily for five days or trimethoprim 300mg once daily for three days as first-line for symptomatic cystitis in adults.

Some data is available for pharmacist-supply.(2) Data from one year after reclassification of trimethoprim across over 100 pharmacies would extrapolate out to a modest 6,380 trimethoprim supplies per year across community pharmacy. While there could be some under-reporting from this research, given the focus was trimethoprim, this is unlikely to have been much of a difficulty, and even if it was 10,000 supplies per year in pharmacy, this would only be 7% of the prescriptions by doctors. This is consistent with the fact that the majority of trimethoprim users have complicating features.(2, 3) The widening of criteria since then could increase those eligible for the service by about a third (based on the New Zealand research). There may have been an increase since then, but anecdotal reports from pharmacy are still that supplies are modest (but greatly appreciated by women), and referral is common. Most of these women would likely have otherwise be prescribed a treatment. Further research as the service matures would be worthwhile.

This data is also consistent with the finding by Braund et al(4) that pharmacists have taken supply seriously, and a verbal confirmation from Medicines Control in late 2017 that checks of trimethoprim screening tool as part of the pharmacy short unannounced audits in 2017 found good compliance.
Gauld et al(2) mapped subsidised trimethoprim supplies against subsidised norfloxacin supplies, finding some increase in trimethoprim as norfloxacin reduced, with the greatest reduction occurring when restrictions on subsidised supply of norfloxacin were implemented in 2014. This is similar to that noted by the Medsafe paper. However, some norfloxacin supplies may also have continued after the subsidy requirements were changed to exclude most women with cystitis, in which case the Pharmaceutical Collection data would not include this information, and this may be why more movement to trimethoprim or nitrofurantoin was not seen.
We are pleased to see that the resistance numbers in 2013-2015 appear stable, and are lower than Australia. In Australia original pack dispensing sees trimethoprim prescriptions for 7 tablets provided, allowing a longer duration of treatment and/or some use on a second occasion without health professional input. This might influence the rates of resistance.

We also note the comments from the Medsafe paper about who is tested. We consider that the urine samples sent for testing could change over time. The BPAC guidelines note that urine culture is not necessary unless there are complicating features. However, based on anecdotal reports, it is likely that testing has included cystitis without complicating features. A reduction over time with messages from BPAC and laboratories that this isn't needed would see an increasing proportion of complicated cases, affecting resistance rates. Likewise, with pharmacist-supply, fewer tests of women with suspected cystitis without complicating features could occur as women treated through the pharmacist would not get a urine test unless they have treatment failure.
We agree with the Medsafe position that there is no need to review the reclassification at this time.
We do note that Appendix 1 is not present in the website version of the Medsafe document, and are pleased to see that Appendices do not always need to be published, given we know that this creates various concerns for applicants and has prevented some applications.

5.4 Manufacturers' original pack – information paper

We support the current flexible approach by the Medicines Classification Committee in which sometimes a manufacturer's approved pack is required, but sometimes it is not. For example, with trimethoprim, the information sheet for pharmacists to give to patients with the pharmacist-supply provides sufficient information for the patient without requiring the manufacturer to produce a specific pack for the relatively small volumes. One time where this requirement could be dropped would be where there is no product available in non-prescription packaging despite a reclassification, and thus access is being impaired. In this case, we would expect that an information sheet could be developed if this is necessary to enable pharmacists to 'prescribe' the product for a specific person but also ensure the patient receives written and verbal information. In addition to this happening in some cases in New Zealand (e.g. trimethoprim, vaccines, oral contraceptives and sildenafil (Douglas only)), Singapore also uses this approach. For some medicines for common indications, use by other household members can sometimes occur, or there could be concerns with intermittent use whereby the patient's medical status may have changed since last use. Therefore, we recommend approved manufacturer packaging is used where specific warnings and precautions are required and expiry dating is present.

We do note the point made (4c) in the paper about personal imports of prescription medicines at the border, and would like to see this expanded at a minimum to pharmacist-only medicines, to ensure a health professional is involved in the supply. Ideally it would be expanded to other medicine classifications also, given the potential for counterfeiting for medicines purchased from the internet, and that pharmacy assistants provide advice (e.g. on doubling doses of paracetamol) and a pharmacist is available in a pharmacy should referral be needed or to intervene where necessary. Some pharmacy-only medicines can be abused, e.g. stimulant laxatives, and the current vigilant stance in pharmacy could be overcome by a purchaser buying large quantities from overseas internet sites. Additionally, we know that pharmacy intervention has provided important and sometimes life-saving referrals with pharmacy-only medicines, including naproxen, omeprazole and paracetamol liquid.(5) The intention of the MCC in classifying a medicine as a pharmacy-only medicine is that the purchase happens in a pharmacy where advice and expertise are available. We have a useful range of medicines available without a prescription in New Zealand, so purchase of unregistered products from overseas provides risk with little benefit.

6.1 Clotrimazole and hydrocortisone to pharmacy-only

We prefer that clotrimazole with 1% hydrocortisone remains a pharmacist-only medicine, rather than change to pharmacy-only medicine.

This product is unusual for consumers with a mismatch of duration of use of ingredients – one that should not be used for more than seven days, and another that should be used for 2-4 weeks to resolve symptoms. We note the labelling instructs usage for up to 7 days followed by use of an antifungal alone for another 14 days. If a patient finds it effective, they may well use the combination product, including 1% hydrocortisone for the full 3 weeks without understanding the rationale for changing if a pharmacist has not explained it to them.

The pharmacist as a health professional can assess skin conditions (symptoms, severity and likely causes), consider other factors about the patient (e.g. age, presence of medical conditions such as immunosuppression or diabetes), consider whether an antifungal-hydrocortisone is the most appropriate treatment (for short-term use), and advise on switching to an antifungal alone to complete treatment. Very importantly, in this assessment the pharmacist is always considering which patients need a medical referral.

Hydrocortisone can reduce skin inflammation so this medicine may appear effective and be used for conditions that are not fungal skin infections. Patients with the irritation and inflammation that this product could be used for from a suspected fungal infection may have scratched the skin increasing the risk of bacterial infection which hydrocortisone should not then be used on.

Canesten is a known name for consumers for nappy rash, so, without the extra safety of the pharmacist-only category (and the consumer's perception of it being a more serious category), this could be used for nappy rash, even if it is not included as an indication on the pack.

A study from the UK where hydrocortisone is pharmacy-only rather than pharmacist-only found off-licence use occurred.(6) Some patients were using non-prescription steroids for rosacea, psoriasis, pruritic vulvae/ani, and vaginal thrush. Ten per cent were applying the product to the face despite instructions not to. Six per cent reported using it for more than 2 weeks. The authors reported: "typically respondents stated that they would continue to use the product for 'as long as necessary' to resolve the condition", indicating they did not realise the short duration that is generally recommended. This study had a low response rate of 16%, and most of the 315 questionnaires were for hydrocortisone alone or Eumovate rather than a combination hydrocortisone-azole which could differ from the other products in usage patterns. While we do not have similar data from New Zealand, we expect that the health professional involvement in every interaction for a 1% hydrocortisone product with a pharmacist-only classification will reduce the incidence of such behaviour.

The Ellis(7) paper mentioned in the application was a random digit phone survey in the US asking about usage of hydrocortisone in the last six months. It would be more prone to recall error than the UK study. This research also had a low response rate – of 7757 eligible households, 2000 agreed to participate, and 458 of these thought they had used hydrocortisone in the last six months. In 14% of cases, the conditions treated were not appropriate. Six per cent of treatments lasted more than 7 days. Treating fungal conditions with a hydrocortisone azole antifungal combination may differ from the usage reported in this study, as the condition lasts longer than 7 days typically, and many will be used to using a product for up to 4 weeks to resolve a fungal condition.

A 15 g pack could be used for a long time on a small area of perioral dermatitis or nappy rash – plenty will be left after 7 days of use. Normally a single 15g pack of clotrimazole is sold for the up to 4 weeks usage required to resolve tinea pedis or tinea corporis, for example, with product remaining after use.
An antifungal plus hydrocortisone is accessible where needed, through the pharmacist. A pharmacist is available without an appointment in a pharmacy, readily accessible to advise someone with a particularly uncomfortable infection (and check to see whether triage to a doctor is necessary or another product is more suitable).
As a health professional, a pharmacist can advise on the need for this combination product supplied, and can explain carefully the need to follow up after 7 days with an antifungal alone, and have the credibility to the consumer. This will maximise best practice and quality use of medicines.

6.2 Loratadine – general sales restriction to six years and older

We recommend that the current restriction of 12 years and older is retained. Children under 12 years would be better managed by the doctor and pharmacist as necessary for optimum quality use of medicines.
Allergies in children can include links with asthma, eczema and anaphylaxis.(8) Parental administration of loratadine to a six year old without a discussion with a doctor or pharmacy staff may miss other related conditions, and not be the most appropriate measure. In particular, a child treated for allergies with loratadine who has undiagnosed asthma will be at risk of poor management which could cause hospitalisation, for example. A recent text on allergies recommended examination with anterior rhinoscopy in children.(9)

Allergic rhinitis causes significant impairment, for example affecting sleep quality which affects daytime alertness and educational achievements,(8) and dysfunction in the family.(9) As a long-term condition, allergies treated poorly in childhood could cause impairment at school for a number of years. Poor treatment of allergic rhinitis affects asthma control.(8, 9) Pharmacy management would likely see a young child referred to the doctor for the most appropriate treatment, which may include a steroid nasal spray, avoidance, or immunotherapy. Intranasal corticosteroids are more effective than antihistamines,(9) but only available on prescription. With purchase of an antihistamine in the supermarket, many parents will not be aware of this option. Furthermore, understanding the basis for the allergy is helpful for its management including allergen avoidance.(8)

6.3 Influenza vaccine – proposal for interns to vaccinate

We are supportive of the submission by the Pharmaceutical Society of New Zealand to allow registered intern pharmacists who have successfully completed the MoH approved vaccinator training course and assessment process to administer Influenza vaccines without the need for a prescription. This will lead to improved uptake of the vaccine and it will increase the pool of frontline vaccinators within primary care. The necessary Standard Operating Procedures are already available within Community Pharmacy for the administration of vaccines and registered intern pharmacists would complete the same vaccination training as all other healthcare professionals. It should be noted that intern pharmacists are registered under the pharmacy council Healthcare Practitioner Competence Assurance Act 2003 and we support that only those intern pharmacists operating under the supervision of a qualified pharmacist who is a vaccinator be eligible to provide the vaccination service.

6.4 Melatonin

If melatonin became a supplement again in New Zealand, this could lead to inappropriate use in children with no health professional involvement. In the US, usage has increased substantially in recent years, including in children. We therefore do not support such availability.

We recommend a reclassification to Prescription only except when supplied by pharmacists who have successfully completed the approved training programme. This would still require that the product is sold according to the licensed indication (primary insomnia in people 55 years and over) and dose and duration (maximum 13 weeks of use). Pharmacists who have undergone additional training and are using a screening tool could be used to ensure triage as appropriate to doctors, and informing doctors of supply (with patient consent), providing only where appropriate. Supply should only be the registered melatonin 2 mg prolonged release medicine which has known quality and action.

6.5 Modified release paracetamol

We are strongly supportive that paracetamol modified release remains a pharmacy only medicine. Modified release paracetamol provides extended pain relief that is important in osteo-arthritis, for example allowing dosing at bedtime to provide coverage through the night and on waking in the morning, or for a day of activity. Pharmacists and pharmacy assistants are extremely well-versed in advising on paracetamol, regularly advising on the appropriate and safe dosing and the need to avoid doubling of ingredients. Research showed this to be a clear priority for pharmacy with liquid paracetamol products,(5) and teaching at pharmacy school and in the Green Cross Health global award winning training academy, Teach Me, emphasizes this for other paracetamol products. There are currently more than 6,000 pharmacy staff enrolled on the Green Cross Health Teach me platform who have access to the paracetamol training tools.

The data in the Medsafe report indicates a low level of calls to the Poisons Centre in New Zealand over a 10 year period. We consider the benefit-risk ratio for paracetamol modified release in New Zealand would be at least as favourable as that found with some other pharmacy-only medicines. We are aware that the main reason that this is being reviewed by Medsafe is due to a decision having been taken relating to a concern in Sweden, and we note significant differences to New Zealand in the indication and poisoning reports. When reviewing data within New Zealand there is a significant difference in the pain for which it is indicated, only being osteo-arthritis. We are also pleased to see that a number of the recommendations made by the MARC review published in December 2017 have already been addressed by the manufacturer.

We understand that the New Zealand Guidelines used at hospitals in New Zealand for paracetamol overdose have included modified release products for many years, which is important to appropriate management. There appears to have been no deaths reported in New Zealand with this product. Training and information sharing by the manufacturer is ongoing with the pharmacy team and the material used is evidence based with key messages around safe, responsible and appropriate use by patients. We suggest that the proposed up- scheduling of paracetamol modified release would affect access for patients who appear to be using the product appropriately

with input from a well skilled pharmacy team that is evidenced in the data provided within the Medsafe documents. We have used training information with pharmacy teams including the pharmacist and will continue to emphasize the importance of ensuring patients understand the maximum six tablets per day dosing and not to double up on ingredients. We know pharmacy is very focused on this already, but we are more than happy to support Medsafe and safe use of medicines.

Conclusion

Thank you once again for the opportunity to comment on agenda items. We are happy to be contacted to clarify any comments or provide the references to the committee if required.
Yours sincerely,

ALISON VAN WYK
Executive, Professional Services
Green Cross Health

Dr NATALIE GAULD
Director
Natalie Gauld Ltd

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MEDICINES CLASSIFICATION COMMITTEE MEETING
To be held in Wellington on 26 April 2018

RESPONSE

to the agenda item 6.5.1 – Modified release Paracetamol proposed reclassification from pharmacy only medicine to restrictive medicine from Medsafe

Introduction

1. The New Zealand Self Medication Industry Association ("**NZSMI**") represents the importers, manufacturers and distributors of the bulk (80%) of New Zealand's over the counter ("**OTC**") product sales in pharmacy, grocery and complementary healthcare outlets. It exists to promote the responsible use of self-medication products. It works closely with Medsafe and other industry bodies to improve the outcomes of the New Zealand health strategy and in particular, the safe and cost-effective use of medicinal products.

NZSMI does not support the Medsafe recommendation

2. The New Zealand public is well served by excellent provision of OTC medicines by a network of well-trained regulated pharmacists and pharmacies which forms the foundation for a world renowned self-care environment. However, we suggest regulators need to support this environment with sensible, risk appropriate legislation to ensure the safety and efficacy of medicines supply.

3. In this instance we do not believe the public is being well served by the proposed change to the availability of modified release paracetamol.

4. MR Paracetamol is a technically advanced, well-researched, widely used product with a high safety margin when used as directed and, in our opinion, does not require specialist pharmacist advice to ensure this safety.

Basis for Medsafe's recommendation

5. It appears from material provided that the basis for the up-scheduling recommendation comes from the June 2016 Article 31 of Directive 2001/93/EU from the medical products agency in Sweden. This report indicates 53 cases of acute overdose, which had highlighted potential inadequacies with the way paracetamol over doses were being treated in Sweden. It appears these protocols were based around immediate release paracetamol products and were proving to be unsuitable for sustained or modified release of paracetamol.

6. This report was then reviewed by the Pharmaco-vigilance Risk Assessment Committee ("**PRAC**") who indicated that over dose treatment procedures developed for IR paracetamol products were not entirely suitable if doctors were not aware that a different dosage form had been ingested. These poor protocols affected decisions such as antidotes to be administered at what point and for how long. PRAC then recommended suspension of modified release paracetamol products from the market.

7. NZSMI concludes that the Swedish situation does not translate well to the New Zealand market as different, more appropriate and specific protocols exist here.

Differences between New Zealand and other markets selling modified release paracetamol

8. Prior to looking at differences in regulation, we believe it is also important to look at the way the PRAC report was presented, discussed and voted on. Only 19 out of the 33 EU member states entitled to vote, voted in favour of this decision.

9. Of more relevance is the fact that the countries where modified release paracetamol is marketed (seven EU countries) the majority voted in favour of retaining the product.

10. It is a concern to us in New Zealand that a number of European countries not marketing modified paracetamol should have such undue influence on the medicines that we have for safe self-medication should, it appears, be so arbitrarily regulated.

11. Of even more significance is our belief that substantial differences in the protocols for the management of paracetamol in Europe and in New Zealand mean the PRAC report should not be given undue influence when deciding on how best to keep New Zealanders safe in this instance.

12. NZSMI contends that we should look more closely at our own situation and then the Australian treatment of modified release paracetamol to make sound regulatory decisions. In Australia the Therapeutics Goods Administration ("**TGA**") has decided not to take any action regarding modified release paracetamol (as recently as December 2017). This market constitutes, we are told, 78% of the global sales of the market leader GSK modified release paracetamol and that this sales dominance results in some one billion tablets being taken in Australia with no fatalities related to MR paracetamol. This is a significant statistical comment given that paracetamol is widely used for those intentionally wishing to harm themselves. Again, indications are that some 319 cases have been recorded in Sweden where the global sales of the market leader constitute 10% of global total as opposed to 78% as mentioned for Australia. (Information supplied by GSK)

13. NZSMI concludes that substantially different over dose and market conditions exist in Europe. We can only surmise that the higher level of patient advice given in Australasian markets and/or variations in packaging and/or patient education have directly translated to our very small incidence of issues surrounding the use of MR paracetamol.

14. NZSMI also understands there are substantial differences in the way overdose is treated in Australasia as opposed to New Zealand, but does not feel sufficiently qualified to make comment in depth on the scientific basis of these protocols except for the observation that they appear to be highly effective when compared to the Swedish studies at reducing harm from modified release paracetamol.

15. Given these substantial differences between the markets we believe the PRAC report and Swedish initiative have been afforded significance far beyond the New Zealand situation.

A Safer Scenario

16. There are numerous education pathways in play surrounding the supply of MR paracetamol and NZSMI would like to promote the concept, in this case, of Education before Legislation.

17. This product improves the lives of a particular patient set by offering a technically advanced dose delivery of a well-known and proven analgesic. To avoid complication it has to be used appropriately and its difference to standard paracetamol noted.

18. Pharmacy staff have a high level of access to training in this product category via suppliers, industry media articles, on-line continuing education courses and pharmacy group

education courses. Package labelling and inserts also inform paitients of the correct way to use these medications.

19. We suggest the MCC recommend suppliers of MR paracetamol be required to review supplied educational material related to this product category to ensure that potential patients are clearly informed about the properties and advantages of this product category and its differences to standard paracetamol.

20. Any review should also target General Practitioners to ensure they are aware of the benefits and risks of this formulation over standard paracetamol.

21. Highlighting these advantages and differences is preferable to restricting access.

22. Further restricting access for patients to a proven modern medicine with a low risk profile (as evidenced by issues recorded over the last ten years by CARM) is not, in our opinion, the best outcome for New Zealand primary healthcare.

As always, NZSMI appreciates the opportunity to have submissions considered.

Scott Milne

Executive Director

New Zealand Self Medication Industry Association

RESPONSE TO AGENDA ITEM TO BE DISCUSSED AT THE 60th MEETING OF THE MEDICINES CLASSIFICATION COMMITTEE, WELLINGTON, 26 APRIL 2018

AGENDA ITEM:

6.5 Modified-release paracetamol – proposed reclassification from pharmacy-only medicine to restricted medicine (Medsafe)

Document type:	GSKCH Response to MCC 60th Meeting Agenda Item 6.5
Submitted by:	[redacted] GlaxoSmithKline Consumer Healthcare, Australia and New Zealand
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Note	Commercially sensitive information has been indicated as such in the submission with the use of red coloured text and bold square parenthesis

Executive Summary

- Modified-release (MR) tablets, containing 665 mg of paracetamol, have been approved and marketed as a pharmacy-only medicine in New Zealand since 2008. The licensed indication for MR paracetamol in New Zealand is "Relief of persistent pain associated with osteoarthritis" These products are supplied in blister packs containing 96 tablets.
- During the 10-year period that MR paracetamol has been available, the New Zealand Pharmacovigilance Centre has identified one case of overdose (non-serious) in which this product was possibly implicated and there have been 31 calls to the National Poisons Information Centre in relation to this medicine. The MARC considered these calls to warrant consideration of the medicines classification of MR paracetamol.
- At its 60th meeting, the Medicines Classification Committee (MCC) is considering the re-classification of MR paracetamol (from pharmacy-only medicine to restricted medicine) on the basis of the recommendation from the Medicines Adverse Reactions Committee (MARC). The MARC review was triggered on the basis of decisions made in Europe. It is the view of GlaxoSmithKline Consumer Healthcare (GSKCH) hat both the manner of supply of MR paracetamol and protocols for the management of potential paracetamol overdose situations in Europe are different to those in New Zealand.
- GSKCH welcomes this discussion, and is confident that the committee will be carefully considering the local evidence in making its recommendation.
- The role of MR paracetamol in the management of osteoarthritis is clearly established. There is a substantial body of clinical evidence to support the conclusion that this medicine has an overall acceptable benefit-risk profile when used to manage mild to moderate pain associated with osteoarthritis.
    - The clinical rationale for using a MR paracetamol formulation is to provide a product with a longer (8-hour) duration of action to facilitate adherence and improved outcomes (Ortiz et al 2016).
    - MR paracetamol is therefore a useful treatment alternative for patients who are unable to take NSAIDs due to tolerability or contraindications, without the need to adhere to the four-times daily dosing schedule required with standard (immediate release, IR) paracetamol.
    - Australian data demonstrates that persistence with MR paracetamol is significantly higher than is that with IR paracetamol, with subsequent benefit that there is less need for patients to escalate up the WHO pain ladder and take stronger pain relievers (Ortiz et al 2016).
- The MARC has identified two core themes upon which consideration of the up-scheduling of MR paracetamol is based:
    A. The complexity of overdose management with MR paracetamol formulations
    B. Concerns around the adequacy of consumer understanding that the dosing with this medicine is different to that with IR paracetamol.

(A): Established local guidelines for overdose management with MR paracetamol are adequate and reliable

- Overdose guidelines designed to specifically address the considerations required with MR paracetamol have been in place in New Zealand since its first launch in this market in 2008 (Fountain et al 2014).
- A review of the awareness, acceptability and application of these guidelines in Dunedin, New Zealand, undertaken in 2011-2012, shows that they are acknowledged as best practice and were applied in 90% or more of overdose cases seen (Fountain et al 2014).
- These Australian and New Zealand paracetamol overdose guidelines state that antidote treatment (with acetylcysteine) should be given to all patients who have ingested an MR paracetamol dose >10 g (Chiew et al 2015). The veracity of this dose-based approach to identifying patients in whom to initiate acetylcysteine is established (see Section 3.1.3).
- By contrast, Swedish guidelines state that antidote treatment (with acetylcysteine) should be given based on where a patient's blood level of paracetamol is relative to a line on a chart (called a nomogram). Under the Swedish guidelines, treatment is only given if serum-paracetamol is above 650 µmol/L at 4 hours, 450 µmol/L at 6 hours, 325 µmol/L at 8 hours or 160 µmol/L at 12 or 18 hours after ingestion. This nomogram line is lower than the line used for managing overdoses with IR paracetamol.
- [A series of analyses has been undertaken, using data from GSK worldwide safety database, to establish the relative effectiveness of the Australian and New Zealand overdose treatment guideline protocols versus those in the Swedish guidelines. These analyses conclude:

  Dataset to 11 December 2016 (83 cases of MR overdose):

  - **Under Australian and New Zealand guidelines**: 80/83 cases reported an acute ingestion of >10 g and therefore acetylcysteine treatment would be recommended in these instances (i.e. **96.4% of cases would have received immediate treatment**).
  - **Under Swedish guidelines**: if the same 83 cases had been managed by plotting their blood paracetamol levels on the nomogram, only 48 cases would have met the criteria for acetylcysteine treatment (i.e. **57.8% of cases would have received immediate treatmen**t).

  Dataset to 12 March 2017 (50 additional cases of MR overdose);

  - Of the 48 cases for which the paracetamol dose ingested was available, 47 reported an acute ingestion of >10 g and therefore using the Australian and New Zealand guidelines acetylcysteine treatment would be recommended in these instances (i.e. **97.9% of cases would have received immediate treatment**).]
- The above analyses are corroborated independently with published Australian data, amongst 116 patients who had ingested a toxic dose (> 10 g) of MR paracetamol over

a period of 8 hours or less (Chiew et al 2018). The majority of those treated in a timely manner were well managed:

- 113 (97%) were commenced on acetylcysteine.
- 21 (18%) patients developed hepatotoxicity, none of these patients required a liver transplant or developed hepatic encephalopathy, and all survived.
- 1 patient without liver toxicity died from respiratory failure secondary to pulmonary aspiration (a condition in which food, liquids, saliva or vomit is breathed into the airways) 30 hours after ingesting MR paracetamol

- These analyses suggest that having a second, lower nomogram line (as in the Swedish protocol) for use in MR paracetamol overdose cases does not identify and treat more patients than using a pre-set toxic cut-off dose (>10g) in conjunction with the single Rumack-Matthew nomogram line (in the manner undertaken in New Zealand).
- Current data (from a GSKCH PK modelling study and from the published Chiew 2018 analysis), alongside the very low reported incidence of overdose cases and an absence of fatalities with MR paracetamol in New Zealand, do not suggest an inadequacy of the current Australian and New Zealand overdose treatment guidelines.

(B): Consumers in New Zealand have adequate understanding regarding dosing with MR paracetamol

- MR paracetamol is well known to the medical community in New Zealand; its use in this setting is supported by Pharmacists and GPs.
- Over the 10-year period that MR paracetamol has been available in New Zealand, there have been a total of 31 calls made to the National Poisons Centre and 38,754,038 tablets sold (or one call for every 1.25 million tablets sold).
- This extremely low ratio of calls to tablets sold suggests, with a high level of confidence, that consumers are aware of and understand the dosing instructions for MR paracetamol.
- The most plausible explanation for the calls to the National Poisons Centre is that the majority of patients are using the product appropriately and that those with questions are actually following the on-pack label guidance to call the Poisons Information Centre if they have any concerns, possibly after-hours when other sources of advice might not be as readily available.
- Risk mitigation measures, such as blister packaging and on-pack paracetamol overdose warnings, have been in place since the product was first launched in 2008. These have since been further supported with ongoing consumer and healthcare professional educational campaigns and the introduction of consumer medicine information leaflets in all GSKCH paracetamol products.
- If there were a problem with patient confusion with the dosing of this MR formulation, a signal would have been seen within the overdose figures. There has been no signal to suggest that mandated Pharmacist-intervention is required to ensure the appropriate use of MR paracetamol.

- Reclassifying MR paracetamol from its current pharmacy-only medicine status to restricted medicine is unlikely to negate the likelihood of a small number of consumers continuing to seek ad-hoc advice from the Poisons Information Centre on its use.

GSKCH believes that retaining MR paracetamol as a pharmacy only medicine is justified based on the following:

- The MARC review has stated that there is no suggestion of a clinical concern regarding MR paracetamol medicines in New Zealand.
- MR paracetamol has an overall acceptable benefit-risk profile when used to manage mild to moderate pain associated with osteoarthritis.
- Accordingly, because MR paracetamol is used for the management of this persistent pain condition:
    - New users are likely to have been recently diagnosed with osteoarthritis and recommended the product by their GP and are therefore purchasing it in an environment where they have access to professional advice.
    - Repeat users will, by default, already be familiar with the medicine and its dosing schedule.
    - Consumers seeking to self-select a MR paracetamol product are paying a significant price premium over and above IR paracetamol, presumably to avail themselves of the longer (8-hour) duration of action and convenience of three-times daily dosing. Hence, they would be highly aware of the appropriate number of doses to be taken.
    - GSKCH has in place an extensive program of training of pharmacists and pharmacy staff (specific to MR paracetamol) to support discussions with consumers in pharmacies (see Section 7.4.2).
- For the majority of users, a more restrictive scheduling is unlikely to add value, but may add a barrier to accessing this medication. This may lead them to revert to using IR paracetamol, which may lead to increased use of other analgesics as was demonstrated in an Australian study (Ortiz et al 2016).
- Overall, the majority of MR paracetamol overdose cases in the GSK safety database (213/319; 67%) have been reported in Sweden. The extent of MR paracetamol abuse observed in Sweden has not been observed in New Zealand:
    - The isolated, non-serious reported case of excess use in New Zealand (5320 mg per day instead of 3990 mg) did not reach the threshold for overdose management requirement (10 g).
    - The dose ingested in this case (8 tablets in a 24 hour period) is significantly lower than in the Swedish case reports,. In Sweden the median dose was reported to be 20 g (range 10-166 g; 15-250 tablets).
- The management of MR paracetamol overdose in Sweden is very different to that in New Zealand. The current Australian and New Zealand guidelines for the treatment of

MR paracetamol overdose are supported by an extensive documented clinical experience. Additional modifications to MR paracetamol overdose guidance, to encompass multiple sampling and an extended period for monitoring appear to be warranted and should be investigated further but do not impact the scheduling status of this medicine. GSKCH is actively seeking to discuss these new data and to collaborate with the local guideline authors to ensure that they are reviewed and updated on the basis of currently available evidence.

- The management of overdose with MR paracetamol is more complex than that with IR paracetamol. However, local guideline have been established and there are no grounds to suppose that emergency rooms in New Zealand might not be aware of MR paracetamol products or that they might not know how to manage overdoses cases with this medicine, should they occur.
- The dosing of MR paracetamol is different to that with IR paracetamol. However, risk mitigation measures are in place and there are no grounds to suppose that patients are confused about its three-times daily dosing regimen and need direct Pharmacist intervention on every occasion of a purchase of this medicine.

Overall conclusion:

- **The local evidence supports the positive benefit-risk profile of MR paracetamol when used as indicated in New Zealand.**
- **There has been no suggestion of clinical concern regarding overdose cases or the management of overdose with MR paracetamol medicines in New Zealand.**
- **Guidelines for the management of MR paracetamol overdose are established and adequate.**
- **Comprehensive risk mitigation measures are in place; consumers have access to information on the appropriate use of MR paracetamol from a variety of sources and educational campaigns reinforce the core message of three-times daily dosing.**
- **A change in classification of MR paracetamol will negatively impact access for legitimate users while placing an unnecessary burden on pharmacists.**
- **The retention of MR paracetamol as a pharmacy-only medicine is justified.**

CONTENTS

1 Introduction

Modified-release (MR) tablets, containing 665 mg of paracetamol, have been approved and marketed as a Pharmacy-Only Medicines in New Zealand since 2008. Currently two such products are marketed in New Zealand: Panadol Osteo Modified-Release 665 mg tablets (GlaxoSmithKline Consumer Healthcare [GSKCH]; approval date: 10/4/2008; TT50-7876) and Paracetamol Osteo-Tab Modified-Release tablets (AFT Pharmaceuticals; approval date: 10/01/2012; TT50-8774). The licensed indication for both medicines is "*Relief of persistent pain associated with osteoarthritis*" and both are supplied in packs containing 96 tablets.

When available in a self-select environment (e.g. Pharmacy-Only Medicine), there are robust data to support that MR paracetamol has an overall acceptable benefit-risk profile when used to manage mild to moderate pain associated with osteoarthritis. MR paracetamol provides the benefits of paracetamol with the convenience of a three times daily dosing regimen (Bacon 2001). The clinical rationale for using an MR paracetamol formulation is to provide a product with an 8-hour duration of action to facilitate adherence and improved outcomes (Ortiz et al 2016). MR paracetamol is therefore a useful treatment alternative for patients who are unable to take non-steroidal anti-inflammatory drugs due to tolerability or contraindications, without the need to adhere to the four-times daily dosing schedule required with standard (immediate release, IR) paracetamol.

Ortiz et al have noted that tablet burden and dose frequency are a barrier to appropriate use in patients who are prescribed IR paracetamol (Ortiz et al 2016). Data from a longitudinal analysis of paracetamol prescribing in Australia over a 2-year period has proven that persistence with MR paracetamol is significantly higher than is that with IR paracetamol, with subsequent impact on less need for escalation up the WHO pain ladder to the use of stronger pain medicines (Ortiz et al 2016).

Overdose guidelines designed to specifically address the considerations required with MR paracetamol have been in place in New Zealand since its first launch in this market in 2008 (Fountain et al 2014). During the 10-year period that MR paracetamol has been available, the New Zealand Pharmacovigilance Centre has identified one case of overdose (non-serious) in which this product was possibly implicated and there have been 31 calls to the National Poisons Information Centre in relation to MR paracetamol.

2 Purpose

From the Medsafe Submission:

"*The Medicines Adverse Reactions Committee (MARC) recommended at its meeting on 7 December 2017 that the Medicines Classification Committee (MCC) considers reclassifying modified-release paracetamol from pharmacy-only medicine to restricted medicine. This recommendation comes following recent regulatory action in Europe to suspend modified-release paracetamol products from the market due to the complexity of managing overdose with these products.*"

2.1 Sponsor's comment

The 60th meeting of the Medicines Classification Committee (MCC) includes an agenda item (item 6.5) to discuss the reclassification of MR paracetamol from pharmacy-only medicine to restricted medicine.

The MCC is considering the re-classification of MR paracetamol on the basis of a recommendation from the Medicines Adverse Reactions Committee (MARC). At its 172nd meeting (December 2017), MARC discussed recent regulatory action in Europe and considered the risk of MR paracetamol overdose. As part of this discussion, MARC reviewed contact data from the New Zealand National Poisons Centre for the period 1 January 2008 to 8 October 2017 and the Swedish pharmacokinetic study by Salmonson *et al.* 2018 – published online 23 June 2017 (Salmonson et al 2018).

The situation in Sweden is very different to that in New Zealand. The MARC review highlights this: "*It should be noted that Medsafe is looking into this issue as a result of overseas regulatory action; there has been no suggestion of a clinical concern regarding modified-release paracetamol products in New Zealand*."

The current agenda item has been raised on the basis of decisions made in Europe wherein the supply of MR paracetamol and protocols for the management of potential overdose situations are different to those in New Zealand. Importantly, many of the cases in the Salmonson paper describe toxicity with MR paracetamol during a time when there was not a specific MR paracetamol overdose protocol and subjects were being treated per the IR paracetamol nomogram. GSKCH welcomes this discussion, and know that the committee will be carefully considering the local evidence, which suggests that there is no safety or public health question to answer with regards to the classification of MR paracetamol in New Zealand.

The remainder of this document provides comment from GSKCH on the issues raised in the agenda item and an evidence base to support why the sponsor considers that Pharmacy-Only status remains a suitable schedule for this product. For ease of navigation the top-level document headings used herein follow those provided in the Medsafe submission, which accompanied Item 6.5 of the 60th MCC meeting agenda.

3 Background

3.1 Paracetamol Overdose

From the Medsafe Submission:

"Overdose with modified-release paracetamol results in a biphasic and prolonged pattern of paracetamol absorption. The standard treatment protocol for paracetamol overdose based on the Rumack-Matthew nomogram may not be adequate to prevent liver toxicity following overdose with modified-release paracetamol [7]."

3.1.1 History of overdose guidelines for MR paracetamol in Australia and New Zealand

Established Australian and New Zealand paracetamol overdose guidelines contain specific and explicit instructions on how to manage overdose with MR paracetamol (Chiew et al 2015). A copy is provided in Appendix 1. These instructions take into account the bi-phasic and prolonged pattern of paracetamol absorption from MR formulations and are distinct from the standard treatment protocol. After very large overdoses, the IR paracetamol formulation demonstrates the same pharmacokinetic profile (per data provided in Appendix 3).

The original paracetamol overdose management guidelines for use in the local market, published in March 1997, were prepared by an Australasian Working Group in consultation with a number of University Hospital groups involved in the clinical management of paracetamol overdose in Australia and New Zealand, and with the Australasian College for Emergency Medicine. The guidelines comprised an explanatory booklet and a wall-chart poster. GSKCH funded this initial program and has maintained updates of the guidelines over several years. The original guidelines were for use in management of overdose with preparations containing IR paracetamol.

In 2001, prior to the Australian launch of 665 mg MR paracetamol, a major revision of the guidelines was undertaken in order to incorporate information about the management of overdose with MR paracetamol formulations. These amendments were based on data extracted from a GSKCH Expert Report on the clinical documentation of MR paracetamol as well as review and comment from Professor Peter Carroll (Pharmacologist) and Dr John Vinen (Emergency Medicine Specialist), both of whom were involved in the development of the original guidelines. Further minor revisions were made in 2002.

In 2005, further amendments were made based on data from an Australian study on the comparative pharmacokinetics of IR and MR paracetamol in a volunteer model of simulated overdose (Tan et al 2006). Dr Andis Graudins (Division of Clinical and Experimental Toxicology, Prince of Wales Hospital, Randwick, NSW, Australia) provided additional expert commentary regarding the appropriate course of action to take in the possibility of overdose with MR paracetamol.

Subsequently, GSKCH convened a meeting in June 2006 to reconcile updated overdose management advice for both IR and MR paracetamol formulations with current Australasian clinical toxicology practice. Revised consensus guidelines were developed by a panel of clinical toxicologists consulting to the Poisons Information Centres in Australia and New Zealand. The draft guidelines were presented for comment at a peer-review clinical toxicology meeting attended by clinical toxicologists from around Australia and New Zealand in January 2007. In 2008, these revised guidelines were published in the *Medical Journal of Australia* (Daly et al 2008).

A feature of the revised guideline was the adoption of a nomogram with a single line. This nomogram line, the Rumack-Matthew nomogram, was initially developed for use with IR paracetamol overdose in the US. The efficacy and safety of acetylcysteine dosing given according to this nomogram has been extensively reviewed and it has been demonstrated to be the treatment threshold which has the most clinical data to support its

efficacy and safety (Smilkstein et al 1988). The adoption of the Rumack-Mathew nomogram in the Australian New Zealand guidelines was based on a desire to simplify decision-making; it lowered the previous Australian/New Zealand nomogram line by 25% so that it reduced the risk for misinterpretation and error. This provides both a margin of safety for patients who may possess risk factors and a small margin of error for estimation of time of ingestion, and avoids the need for potentially confusing additional lines (Daly et al 2008). The Swedish guidelines have two lines, the lower of which is used for patients presenting the MR paracetamol overdose. This is a fundamental difference compared with the local paracetamol overdose guidelines. However, the Australian and New Zealand toxicology experts agreed that having two lines was confusing, hence the reason for having only the one in the local guidelines.

The revised guidelines further updated advice on the management of staggered paracetamol overdose and on overdose with MR paracetamol. This updated version of the paracetamol overdose management guidelines was in place when MR paracetamol was launched in New Zealand in 2008.

Most recently, the guidelines were further updated, independently of GSKCH, using a similar process to that described above. These updated guidelines were published in the *Medical Journal of Australia* in 2015 (Chiew et al 2015). The key changes from the previous guidelines released in 2008 are recommendations for management of liquid paracetamol ingestion in children, management of patients with large/massive overdoses, duration of acetylcysteine treatment in MR paracetamol ingestions, repeated supratherapeutic ingestions and indications for activated charcoal.

Within the current Australia and New Zealand Paracetamol overdose guidelines (Appendix 1), the guidance for overdose with MR paracetamol is as follows (Chiew et al 2015):

- If more than 10 g or 200 mg/kg (whichever is less) has been ingested, **commence acetylcysteine**.
- Measure serum paracetamol concentration at 4 or more hours post-ingestion, then again 4 hours later if the first concentration is below the nomogram line.
- If serial paracetamol concentrations taken 4 hours apart are below the nomogram line **and decreasing**, acetylcysteine may be discontinued, otherwise continue the full 21-hour course of acetylcysteine to its completion.
- If < 10 g and < 200 mg/kg has been ingested, measure serum paracetamol levels to determine the need for acetylcysteine. Serum paracetamol concentrations should be taken at 4 hours or more post-ingestion (as with IR paracetamol preparations) and repeated 4 hours later. If either concentration is above the nomogram intervention line, acetylcysteine should be commenced.
- Near the planned completion of acetylcysteine infusion, a repeat ALT and paracetamol concentration should be measured. Treatment with acetylcysteine should be continued if the ALT is increasing (> 50 U/L) or the paracetamol concentration is greater than 10 mg/L (66 μmol/L). Acetylcysteine can be continued at a rate of 100 mg/kg of acetylcysteine in 1000 mL of 5% dextrose over 16 hours.

3.1.2 Overdose guidelines for MR paracetamol in Sweden

The Swedish guidelines for the management of paracetamol poisoning in Sweden were revised in 2016 to include advice on managing overdose with MR paracetamol following discussion of the Swedish case data (Hojer et al 2016), and adopted formally in January 2017 (Appendix 2).

Single toxic dose amounts in adults and children are 140 and 175 mg/kg, respectively. Blood sampling for serum paracetamol measurement is recommended 4 h post ingestion. Urgent blood sampling is recommended for those patients presenting >4 h post ingestion. **Blood sampling is recommended before initiation of treatment with N-acetylcysteine.** The rationale cited by these guidelines is the potential for acetylcysteine to cause false low values for serum paracetamol.

In MR paracetamol overdose, blood sampling is recommended at 4, 6, 12 and 18 h (even though acetylcysteine treatment may be in progress for the later time points) post paracetamol ingestion. A high (not defined) serum paracetamol concentration late (not defined) in the time course of sampling is justification for a dose increase in acetylcysteine. Rising serum paracetamol concentrations but falling below the nomogram treatment line are a justification for more frequent blood sampling.

Threshold values for serum paracetamol indicating that acetylcysteine treatment should be commenced in paracetamol overdose are lower for MR paracetamol overdose than for IR paracetamol overdose at all time points, creating a nomogram with two threshold lines. There is no difference between the initial acetylcysteine bolus dose between MR and IR paracetamol overdose protocols. The maintenance therapy for the MR paracetamol overdose patient is acetylcysteine at 12.5 mg/kg for 20 h, with a stop rule that serum paracetamol is undetectable.

A key limitation of the Swedish protocol is that it relies on the intoxicated patient for time of ingested dose and acetylcysteine treatment can be delayed until serum paracetamol levels are known. Lowering the threshold level of serum paracetamol at which acetylcysteine treatment commences ensures more MR paracetamol overdose patients receive acetylcysteine treatment, but also relies on the intoxicated patient to be able to provide information about the paracetamol product that was taken.

3.1.3 Comparison of overdose guidelines for MR paracetamol

The antidote, acetylcysteine, is effective if initiated early (within 8 h after an acute ingestion); its use minimises morbidity from paracetamol overdose (Daly et al 2008). One of the main concerns with managing overdose after MR paracetamol formulations is the issue of late nomogram line crossers. With MR paracetamol the initial presence of concentrations below the nomogram line within the designated 4-8 hour window appears to reject the need for antidote treatment only to cross the nomogram line at a later point in time, resulting in late initiation of antidote intervention.

To account for this, the Swedish guidelines have introduced a second, lower, line at which patients who have taken an overdose of MR paracetamol should be treated. This appears to suggest that the Swedish guidelines are more conservative than those currently established in Australia and New Zealand. However, this is not the case because the Swedish guideline relies on patient report (of whether IR or MR paracetamol was taken for the overdose) and a serum paracetamol concentration to be measured.

The following table provides a summary comparison of the key elements of the current MR paracetamol overdose protocols in Australia and New Zealand versus those in Sweden.

Table 1. MR paracetamol overdose protocols: Australia and New Zealand versus Sweden

	Australia & New Zealand	**Sweden**
Single toxic dose stated	Yes: 10 g	Yes: 140 mg/kg
Stated threshold for starting acetylcysteine treatment	Yes: overdoses of 10 g or 200 mg/kg (whichever is less)	No
Nomogram	Single line Rumack-Matthew Note: Previous versions had a second (lower) line for "high risk" patients. This was removed in the 2008 guidelines because it was deemed to introduce unnecessary complexity to clinical risk assessment (Daly et al 2008)	Two lines, the lower line to be used for assessing MR paracetamol overdose Note: Second line corresponds to the "high risk" line previously removed from the Australia & New Zealand guidelines
Serum paracetamol measurements	Yes: 4 and 8 hours post-ingestion	Yes: 4, 6, 12 and 18 hours post-ingestion
Blood sampling before initiating acetylcysteine	Not required if the ingested dose is above 10 g	Yes: due to potential for acetylcysteine to cause false low values for serum paracetamol

[A series of analyses has been undertaken, using data from GSK worldwide safety database, to establish the relative effectiveness of these two protocols.

Analysis 1: Dataset to 11 December 2016.

- As of 11 December 2016, the GSK worldwide safety database contained a total of 83 cases of MR paracetamol overdose associated with drug-related hepatic disorders with sufficient information for assessment. The dose ingested was available for all 83 cases, and ranged from 6.6-166 g. Country of origin of these cases was Sweden (n=72) and Australia (n=9).
- In accordance with the established Australian and New Zealand paracetamol overdose guidelines all patients are administered acetylcysteine if ingestion of >10 g sustained release formulations are suspected. Of the above 83 cases, 80 reported an acute ingestion of >10 g and therefore acetylcysteine treatment would be recommended in these instances (**i.e. 96.4% of cases would have received immediate treatment**).
- By contrast, utilising the current Swedish guidelines, for sustained release formulations acetylcysteine is administered if serum-paracetamol is above 650 µmol/L at 4 hours, 450 at 6 hours, 325 at 8 hours or 160 µmol/L at 12 or 18 hours after ingestion. In accordance with the nomogram, only 48 cases would have met the criteria for acetylcysteine treatment (**i.e. 57.8% of cases would have received immediate treatment**).

Analysis 2: Late line crossers

- Late line crossers are defined as patients whose early serum paracetamol measurements were below the acetylcysteine treatment line but whose serum paracetamol later rose and crossed this treatment line.
- Further analysis of the 11 December 2016 dataset, showed that when late line crossing is determined using the Rumack-Matthew nomogram, 28 of the 83 cases of overdose with MR paracetamol would be classed as 'late line crossers'.
- However if the Swedish treatment guidelines were applied this is reduced to 6 cases. Only 21% (6/28) cases of late line crossing are identified using the Swedish guidelines compared to those identified using the Rumack-Matthew nomogram in the Australian and New Zealand paracetamol overdose treatment guidelines.

Analysis 3: Dataset to 12 March 2017

- As of 12 March 2017, there were an additional 50 cases of MR paracetamol overdose associated with drug-related hepatic disorders with sufficient information for assessment. The dose ingested was available for 48 cases, and ranged from 8-166 g. Country of origin of these cases was Sweden (n=43) and Australia (n=7).
- Of the above 48 cases, 47 reported an acute ingestion of >10 g and therefore acetylcysteine treatment would be recommended in these instances using in the Australia/New Zealand paracetamol overdose treatment guidelines (**i.e. 97.9% of cases would have received immediate treatment**).]

3.1.4 Sponsor's comment

Medsafe has raised concern that the standard treatment protocol for paracetamol overdose based on the Rumack-Matthew nomogram may not be adequate to prevent liver toxicity following overdose with MR paracetamol.

As shown above (section 3.1.3) analysis of the GSK safety database supports that the standard protocol established in New Zealand is both adequate and highly effective in managing MR paracetamol overdose. This is corroborated independently with Australian data (Chiew et al 2018). In a 4.5 year prospective observational study, Chiew et al describe the clinical characteristics and outcomes in 116 patients who had ingested a toxic dose (> 10 g) of MR paracetamol over a period of 8 hours or less. Of these 116 patients 113 (97%) were commenced on acetylcysteine. The majority of those treated in a timely manner were spared toxicity: 21/116 (18%) patients developed hepatotoxicity; none of these patients required a liver transplant or developed hepatic encephalopathy, and all survived.

Having a second, lower nomogram line (as in the Swedish protocol) for use in MR paracetamol overdose cases does not identify and treat more patients than using a pre-set toxic cut-off dose (>10g) in conjunction with the single Rumack-Matthew nomogram line.

The current guidelines for the management of MR paracetamol overdose in Australia and New Zealand have been established since the launch of the product. Decisions made in Europe, underscored by there being no approved protocol for the management of MR paracetamol overdose across the EU, do not provide a relevant basis upon which local regulatory decisions should be made in New Zealand, where the evidence confirms that there are long-standing and effective overdose guidelines in place.

3.2 Previous discussions by MCC concerning modified-release paracetamol

From the Medsafe Submission:

"On 9 June 2006, the MCC acknowledged that 665 mg tablets had been available in Australia for four years without evidence of significant problems related to overuse or overdose, but expressed ongoing concern that emergency rooms might not be aware of modified-release paracetamol products, and of the need to retest patients with equivocal blood paracetamol levels following overdose."

3.2.1 Distribution of MR paracetamol overdose guidelines and education in New Zealand

As described above, the 2008 iteration of the Australian and New Zealand paracetamol overdose guidelines was an extensive revision undertaken to capture the relevancy of new data regarding overdose with MR paracetamol formulations. Until this point in time, the guidelines had been distributed to hospital emergency departments across Australia and

New Zealand in the form of a booklet and accompanying poster.

The change in format, introduction of a new more conservative nomogram and additional instruction relating to MR paracetamol in this revised set of guidelines was deemed of importance in the toxicology community (Fountain et al 2014). As such the proposed changes were presented to members at the 2007 meeting of the Australasian Society for Emergency Medicine (ASEM) to obtain feedback prior to their finalisation.

Upon finalisation, a number of activities were undertaken to ensure their wide-spread dissemination to relevant medical practitioners (Fountain et al 2014). The revised guidelines were:

- Published in the "Toxicology Handbook"
- Published on the Australasian Society for Emergency Medicine (ASEM) website (http://www.asem.org.au)
- Provided in print and electronic formats to all hospital A&E departments in New Zealand and Australia
- Graphics of the treatment algorithms were provided as separate files for ease of access and use in hospital computer-based retrieval systems.
- Internet access to these guidelines in New Zealand was provided through www.toxinz.com
- Published in the Medical Journal of Australia and presented at conferences.
- Presented to medical toxicologists in New Zealand via annual clinical toxicology workshops.

A review of the awareness, acceptability and application of these guidelines in Dunedin, New Zealand, undertaken in 2011-2012, shows that they are acknowledged as best practice and were applied in 90% or more of overdose cases seen (Fountain et al 2014). This study analysed data from 100 consecutive paracetamol overdose presentations, 95 were with IR paracetamol and 5 with paediatric formulations. Not all patients were managed strictly per the guidelines, with the most common deviation being that additional tests were ordered. Junior doctors ordered the majority of these excess tests, reflecting their lack of clinical experience rather than any failing of the guidelines.

3.2.2 Sponsor's comment

The MCC previously considered the scheduling of MR paracetamol at the 34th meeting (June 2006). It considered carefully the potential for differing risk compared to immediate release. It recommended a reclassification to pharmacy-only medicine category on the proviso that emergency department guidelines be prepared and circulated which would take into account the MR paracetamol products.

As described in Section 3.1.1, GSKCH fulfilled on an ongoing basis its commitment to prepare and promote a protocol for the treatment of paracetamol overdose in emergency rooms which takes into account the treatment required for slow release forms. Importantly the evidence in New Zealand, a single recorded incidence of overdose (non-serious) over the 10 years that MR paracetamol has been available, would suggest that the recommendation by the MCC at the 34th meeting was an appropriate one.

The Medsafe document accompanying the current 60th MCC meeting agenda provides a number of statistics regarding overdose with paracetamol and calls to the NZ National Poisons Centre (cf "*Paracetamol is the single most common drug taken in overdose leading to hospital presentation and admission, accounting for 22.4% of poisonings presenting to New Zealand public hospitals")*. Despite a high volume of calls and hospital visits, the New Zealand Pharmacovigilance Centre has identified only one case of overdose in which MR paracetamol is possibly implicated. There have been no recorded deaths associated with the use of MR paracetamol in New Zealand. Similarly, only a very small proportion of calls to National Poisons Centre in Zealand (31 calls in 10 years) relate to MR paracetamol – these calls are addressed in detail in Section 6.2.

These statistics provide support of the high-level of awareness of the specific needs for managing potential overdose with MR paracetamol in New Zealand. There are no grounds to suppose that emergency rooms in New Zealand might not be aware of MR paracetamol products or that patients are confused and need direct Pharmacist intervention on every occasion of a purchase of MR paracetamol. Should there have been a problem with patient confusion with this medicine that would warrant mandated Pharmacist-intervention, it would have been expected to be apparent within the overdose figures.

Overdose with paracetamol is either accidental (typically in children with liquid formulations) or intended (typically in adults). The best way to reduce the risk of accidental overdose is through advice on correct dosing in the product labelling, keeping the medicines out of reach of children (a statement present on the front of pack), and avoiding taking multiple paracetamol products (also stated on pack). This is something that New Zealand community pharmacy is very aware of and active in (Gauld & Sullivan, unpublished research). It is at the emergency room where the importance of the MR paracetamol product needs to be considered, and as evidenced from the Dunedin study (Fountain et al 2014), this has been well addressed in New Zealand.

4 Recent international regulatory actions

4.1 Europe

Medsafe Submission:

The PRAC could not identify a way to minimise the risk to patients, or a feasible and standardised way to adapt the management of paracetamol overdose across the EU to allow for treatment of cases that involve modified-release preparations, and therefore recommended that the marketing authorisation for modified-release paracetamol-containing products be suspended.

The PRAC's recommendation was endorsed by the Co-ordination Group for Mutual Recognition and Decentralised Procedures – Human (CMDh)[i], and is now before the European Commission to issue a final legally binding decision that will be valid throughout the eU[ii].

4.1.1 Brief overview of the MR paracetamol review undertaken in Europe

On 30 June 2016, a referral under Article 31 of Directive 2001/83/EU was initiated for MR paracetamol-containing tablets at the request of Sweden's Medical Products Agency, following 53 reported cases of acute overdose which had highlighted potential inadequacies with the standard paracetamol poisoning treatment protocol (the Salmonson data) (Salmonson et al 2018). At the time that these cases occurred in Sweden, the standard procedures for assessing and managing overdose and poisoning with paracetamol had been established based only on IR paracetamol products.

Subsequent to this referral, the European Medicines Agency (EMA) Pharmacovigilance Risk Assessment Committee (PRAC) reviewed the benefits and risks of MR paracetamol tablets, to evaluate available evidence to determine the risk of overdose with these paracetamol formulations, and whether any additional measures need to be taken. The outcome of this review has been a recommendation to suspend MR paracetamol products from the market, although it was recognised there were no issues with MR paracetamol preparations when used in accordance with their product information. The rationale behind this recommendation was that in overdose the usual treatment procedures developed for IR paracetamol products are not appropriate, and that if doctors are not aware that a MR paracetamol formulation has been ingested, which affects decisions such as when and for how long to give an antidote, overdose might result in severe liver damage or death. Furthermore, it was not possible to agree a feasible and standardised way to adapt the management of overdose across the EU to cover both IR and MR paracetamol products.

This matter was referred to the Coordination Group for Mutual Recognition and Decentralised Procedures–- Human (CMDh), in December 2017, which supported the recommendation. A subsequent referral to the European Commission (EU), for a final binding decision, confirmed the decision in February 2018. National Health Authorities are expected to suspend the marketing authorisations for MR paracetamol products over coming months. The timetable and method of implementing the suspension will be set individually by the local Health Authority in the EU where the product is licensed. These marketing suspensions can be lifted if marketing authorisation holders can provide evidence of appropriate and practical measures to help prevent overdose with these products and adequately reduce its risks.

4.1.2 Important details pertaining to voting by PRAC and CMDh

Voting information available from the PRAC and CMDh indicates that 19/33 (57.6%) of the PRAC votes and 15/28 (53.6%) of the CMDh member states were in favour of the recommendation to suspend the marketing authorisation for MR paracetamol and that a majority was only marginally reached in both cases. Of note, MR paracetamol is marketed in seven EU countries and of these five voted in favour of retaining the product. Hence aside from Sweden, the market that had initially instigated the PRAC review only one other market in which MR paracetamol products are marketed voted in favour of suspending its marketing authorisation.

The management of MR paracetamol overdose in Sweden in particular (and lack of uniformity across Europe) is different to the effective and long established procedures and positive outcomes in New Zealand. On this basis, GSKCH assert that actions taken in the EU have little bearing on decision making locally. The potential negative impact of restricting access to MR paracetamol in New Zealand, on both patients and Pharmacists, is not warranted.

The background for the EU decision, that a single EU member state drove a change that most countries with MR paracetamol disagreed with, is particularly informative for the New Zealand consideration. The additional effective and long-established procedures and positive outcomes in New Zealand, and the careful consideration of the MCC of this aspect of the medicine when first reclassified would support that the current status seems reasonable.

4.1.3 Current comparable regulators position outside of the EU

The PRAC decision does not directly affect markets outside of EU. Despite the PRAC review, MR paracetamol continues to be available in major markets outside the EU.

Australia:

- The sponsor has kept the Therapeutic Goods Administration (TGA) of Australia appraised of events in the EU, as it has Medsafe, since the initial PRAC announcements in September 2017.
- There has been only one death reported in Australia in association with paracetamol MR (an 87-year old man who died from respiratory failure secondary to aspiration 30 h post-ingestion of MR paracetamol) (Chiew et al 2018). There have been no deaths in patients who have developed hepatotoxicity subsequent to MR paracetamol overdose (Graudins 2014, Chiew et al 2018), and the number of toxic cases is proportionally lower compared to Sweden. [This is of relevance given that Australia constitutes the highest proportion of GSKCH MR paracetamol sales globally (78%) comprising some one billion tablets annually.]
- At the present time, the TGA has not elected to take any action regarding MR paracetamol products (most recent correspondence dated 21 December 2017).

USA:

- In the USA, several brands of MR paracetamol (650 mg paracetamol/tablet) have been available for over two decades in a general sales environment. None of these US products are marketed by GSKCH.
- An extensive review of paracetamol, undertaken by the US Food and Drug Administration, resulted in regulatory action to restrict the amount of paracetamol per dosage unit in prescription medicines, many of which are co-formulated with narcotic analgesics. These changes did not affect non-prescription medicines.
- The US literature reports only two MR paracetamol-related fatalities, out of a total of 3003 overdose cases; the exact cause of death was not confirmed in either case (Dart et al 2005).

- As with the Australian and New Zealand paracetamol overdose guidelines, similar guidelines in the US have been long established to manage modified release paracetamol.

Switzerland (SwissMedic):

- Whilst located in Europe the Swiss are not bound by EU decisions.
- At this time MR paracetamol remains a prescription medicine in this market and GSKCH has informed the local health authority of the EU decision.

4.1.4 Sponsor's comment

There are robust data to support that MR paracetamol has an overall acceptable benefit-risk profile when used to manage mild to moderate pain associated with osteoarthritis. To date, because of long established and effective guidelines and little evidence of misuse of MR paracetamol, no other medicines regulators where the product is marketed have elected to take any action to restrict availability of this valuable medicine.

5 Scientific information

5.1 Pharmacokinetics of modified-release paracetamol

Medsafe Submission:

The paracetamol treatment nomogram may not, therefore, reliably predict hepatotoxicity following overdose with modified-release paracetamol formulations.

5.1.1 Adequate local guidelines are established and reliable

Amongst patients who have had an overdose with MR paracetamol, longer time to initiation of acetylcysteine treatment is associated with a significant increased risk of hepatotoxicity (Chiew et al 2018). Since 2001, the Australian and New Zealand guidelines have offered advice for the management of overdose of MR paracetamol, and in 2008 were updated to include the specific advice that acetylcysteine treatment should be started immediately if more than 200 mg/kg or 10 g (whichever is less) has been ingested (Daly et al 2008).

Tan and Graudins recognised the potential for slow absorption of MR paracetamol and thus a delayed peak serum paracetamol concentration above the nomogram line, and concluded that the paracetamol treatment nomogram might not reliably predict hepatotoxicity (Tan et al 2006). The more recent 2015 update of the Australian and New Zealand guidelines offers further guidance in which serial paracetamol and alanine aminotransferase concentrations are used to determine the duration of acetylcysteine treatment in MR paracetamol overdose (Chiew et al 2015).

[Data from a PK modelling study undertaken by GSKCH (Appendix 3) using

simulations of overdoses of 10, 15, 25, and 50 g of MR paracetamol indicates that at all such doses, serum paracetamol may cross the Rumack-Matthew treatment nomogram line at some point within 24 hours of ingestion, even if this is not apparent at 4 hours.]

For this reason, treatment with acetylcysteine should be considered in anyone who is suspected to have taken an overdose of MR paracetamol or unknown paracetamol tablet of 10 g or more, rather than relying solely on measurements of serum paracetamol to determine whether or not to treat with acetylcysteine. This allows for a timely initiation of antidote, which is crucial for a positive response, as shown in the 2018 study by Chiew et al (see below).

This dose-based approach is consistent with the published Guidelines for the management of paracetamol poisoning in Australia and New Zealand (Chiew et al 2015). As previously stated (Section 3.1.3), analyses undertaken using data from GSK worldwide safety database has established the veracity of this approach in identifying patients in whom to initiate acetylcysteine:

- [Safety dataset to 11 December 2016: 80/83 (96.4%) MR paracetamol overdose cases would have received immediate treatment.
- Safety dataset to 12 March 2017: 47/48 (97.9%) MR paracetamol overdose cases would have received immediate treatment).]

Recently published data, based on a prospective review of 116 MR paracetamol overdose cases in Australia, reported that 21 cases (18%) developed hepatotoxicity (Chiew et al 2018). These patients had a significantly longer time to treatment than those who did not develop hepatotoxicity (16.5 versus 4.5 hours, $p<0.0001$).. None of these patients required a liver transplant or hepatic encephalopathy, and all survived.

5.1.2 Sponsor's comment

The established treatment paradigm for paracetamol poisoning in Australia and New Zealand is that overdoses above 10 g should be treated immediately without waiting for results from paracetamol concentration analysis (Chiew et al 2015).

The results from the PK modelling study, undertaken by GSKCH (Appendix 3), indicate that further additions to optimise the existing protocol for treatment of overdose with MR paracetamol may be warranted.

- Multiple sampling – GSKCH recommends that blood samples to measure serum paracetamol levels should be taken 4, 6 and 8 hours after ingestion (not 4 and 8 as in the existing Australian and New Zealand guidelines). GSKCH is discussing the utility of calculating paracetamol half-lives in the management of overdose with Poisons Information Centres as this is not a routine part of current clinical practice. The use of half-lives represents a novel approach for the management of paracetamol overdose, which allows for earlier detection for the need for treatment with antidote, which may further improve the outcomes of patients in an overdose setting.
- Time period for monitoring – Due to elevated serum paracetamol concentrations

extending for up to 48 h, GSKCH recommends that patients who have ingested MR paracetamol should be adequately monitored. Moreover, where dose, time of ingestion, or formulation is not known, patients should be treated with antidote immediately while continuing to monitor paracetamol concentrations and signs of hepatic injury. Monitoring and treatment with acetylcysteine should continue until serum paracetamol levels and liver functions have normalised.

These results are corroborated independently by the recommendation of Chiew et al, that patients with large (≥ 40 g) acute overdoses of MR paracetamol have repeat paracetamol concentrations to guide increased and prolonged administration of acetylcysteine and/or repeated doses of activated charcoal (Chiew et al 2018).

Current data from the GSKCH PK modelling study and from the Chiew et al 2018 analysis, alongside the very low reported incidence of overdose cases and an absence of fatalities with MR paracetamol in New Zealand, do not suggest an inadequacy of the current Australian and New Zealand guidelines. Rather they underscore opportunities to further refine the protocols for managing overdose with MR paracetamol.

GSKCH is actively seeking to discuss these new data and to collaborate with the local guideline authors to ensure that they are reviewed and updated on the basis of currently available evidence.

5.2 Swedish Data (Salmonson et al, 2018)

Medsafe Submission:

The authors concluded that the serum paracetamol-time profile following overdose with modified-release paracetamol is characterised by prolonged absorption with delayed maximum serum concentrations. Persistent high levels of paracetamol were observed, clearly correlated to increasing doses. The standard treatment protocol, based on experiences with immediate-release paracetamol, was insufficient to prevent development of liver damage especially in the cases with persistent high serum levels.

5.2.1 Limitations of the Salmonson data set

A key limitation of the Swedish protocol is that it relies on the intoxicated patient to relate the time of ingested dose and acetylcysteine treatment can be delayed until serum-paracetamol levels are known. The conclusions from the Salmonson dataset, published online 23 June 2017 (Salmonson et al 2018), which evaluated outcomes based on an older Swedish protocol with no specific guidelines for MR paracetamol, highlight the inadequacy of using an overdose protocol designed for use with IR paracetamol in response to an overdose with an MR paracetamol product.

The Salmonson dataset reviewed data from 145 medical records and included 53 cases in which acute ingestions of MR paracetamol greater than 10 g had been documented

(Salmonson et al 2018). The median reported dose was 20 g (range 10–166 166 g). None of the patients required a liver transplantation. No fatalities were reported.

Had the Australian and New Zealand guidelines been applied to these cases, treatment with acetylcysteine would have been initiated in **all 53 of these cases** at the time of admission. However, Salmonson et al. report that:

- Only 43 (81%) patients received acetylcysteine.
- Acetylcysteine was commenced within 8 hours in 34 (64%) patients.
- Eleven (21%) patients had serum alanine aminotransferase levels above the reference range at 24 hours:
  - Only 7 of these patients received acetylcysteine within 8 hours of ingestion and 3 developed liver toxicity.
  - A further 6 out of these 11 patients developed hepatotoxicity with alanine aminotransferase >1000 IU/L.

5.2.2 Literature supports high level of recovery even in overdose

A comprehensive literature search was conducted that focused on toxicity associated with paracetamol controlled release formulations, irrespective of manufacturer. The following keywords were used for the search: 'paracetamol toxicity' and 'controlled release formulations'. A total of 53 articles were yielded, and were reviewed to determine those relating to overdose. The relevant articles (excluding the previously discussed Salmonson dataset) are summarized below with key attention on clinical/ laboratory findings and outcome (mortality/ morbidly) in overdose experiences.

Several case series, in which overdose with 665 mg MR paracetamol have been reported, are documented in the literature. The majority of cases of paracetamol MR overdose described in published literature show clinical/laboratory effects of increased liver enzymes, increases in prothrombin time, severe hepatotoxicity (alanine aminotransferase >1000 IU/L) or acute liver failure.

The treatments offered to patients who had ingested overdoses vary by country, according to local guidelines. The majority of these case reports (summarised below) originate from Australia (noting that the MARC review has established that there is only one recorded MR paracetamol overdose ever recorded in New Zealand in the 10 years such a product has been in the market, and no treatment was deemed necessary). Here, the established Australian and New Zealand overdose treatment protocols were sufficient to prevent any serious outcomes associated with paracetamol overdose.

- Dart et al 2005 [USA] published a review looking at the safety of paracetamol 650 mg MR both at the therapeutic dose and in overdose. In their review the authors described two fatal cases associated with ingestion of paracetamol MR reported in the Toxic Exposure Surveillance System database (TESS) between 1994 and 2002, however the exact cause of death was not confirmed in either case. During this time, there were a total of 3003 cases in which a paracetamol MR product was identified (Dart et al 2005).

- Roberts and Buckley 2008 [Australia] described the clinical course of a 25 year old female patient (B0500680A) who acutely ingested 96 (64g) tablets of 665 mg MR paracetamol. The patient presented at 14.5 hours post ingestion with a paracetamol concentration of 2235 μmol/L. Treatment was provided with anti-emetics and acetylcysteine, with blood sampling every 6 hours to guide treatment. The patient remained clinically well throughout her experience (Roberts et al 2008).
- Graudins et al 2009 [Australia] presented a report (B0591340A) from Australia, concerning a 72 year old female patient whom following acute ingestion (79 g) of 665 mg MR paracetamol presented with dual peaks in paracetamol serum concentration, and elevation in liver enzymes which resolved following treatment. The authors in this case postulated that the dual peaks resulted from the sequential release of drug firstly from the immediate release fraction of the tablet and then the modified-release fraction (Graudins et al 2009).
- Graudins et al 2010 [Australia] presented a case series of 4 patients who experienced acute intoxication, 2 (B0493857A, B0506468A) of whom had received 665 mg MR paracetamol tablets. In this case series, paracetamol concentrations showed an initial plateau absorption phase in the first 6–8 hours post ingestion and then remained persistently elevated above the paracetamol treatment nomogram line during the following 16–18 hours post ingestion. It was noted that both patients recovered following treatment (Graudins et al 2010).
- Graudins 2014 [Australia] conducted a retrospective review of 665 mg MR paracetamol poisonings occurring at the Monash Health Emergency Department, Australia between 1 October 2009 and 30 September 2013 to determine if the management of identified cases was consistent with existing guidelines. Graudins identified 42 cases of MR paracetamol overdose, of which 5 patients (B1008372A, B1008411A, B1008412A, B1008413A, B1008414A) developed non-serious alanine aminotransferase elevations which resolved following treatment. There were no patients with acute liver failure and no fatalities were noted. From this retrospective review Graudins notes most patients presenting with MR paracetamol poisoning requiring acetylcysteine treatment had an initial serum paracetamol concentration indicating the need for treatment. The current Australian and New Zealand nomogram for paracetamol poisoning would have detected all cases requiring acetylcysteine treatment (Graudins 2014).
- Tellerup et al 2016 [Sweden] described a case (SE2016082274) of liver damage following an overdose of paracetamol, in a 48 year old male patient who ingested 66.5g of 665 mg MR paracetamol. One hour following ingestion, he presented to the hospital with an initial paracetamol concentration of 1032 mmol/L, with normal liver function tests, acetylcysteine was started immediately, 18 hours post admission paracetamol concentrations rose to 2871 mmol/L and a second course of acetylcysteine treatment was

commenced. The patient developed liver damage with a peak alanine aminotransferase of 111 μkat/L (6660 U/L) at 113 hours (INR 2.0). The outcome for this patient was not reported (Tellerup et al 2016).

- Chiew et al, 2017a [Australia; The Australian Paracetamol Project] conducted a prospective observational study conducted with a focus on paracetamol MR overdose and associated liver injury and its treatment. Of 54 patients recruited within a study period of three years, 18 showed an increase in alanine aminotransferase > 50 U/L. Of these 18 patients, 10 patients further developed hepatotoxicity (alanine aminotransferase >1000 U/L). Chiew et al conclude that following acute overdose of MR paracetamol patients may have persistently high paracetamol concentrations for >24 hours. Paracetamol concentrations can be erratic with double or delayed paracetamol peaks. Later doses of acetylcysteine may need to be increased in patients with persistently high paracetamol concentrations. The median paracetamol dose was 31.9g, no fatalities were reported.
- Schultz et al, 2017 [Denmark] evaluated all enquiries received in the Danish Poison Information Centre (DPIC) involving ingestion of paracetamol MR. A total of 113 enquiries were received over a period of 10 years, including cases of suicidal attempts (n = 37) and medication errors (n=32). Of these 113 cases, 58 were classified in the two most severe classes of severity. Another 37 cases were classified into two classes with less severity or no risk of poisoning. The median paracetamol dose was 12g, no fatalities were reported (Schultz et al 2017).
- Chiew et al, 2018 [Australia; Australian Toxicology Monitoring (ATOM)] conducted a prospective observational study to describe the clinical characteristics and outcomes of acute MR paracetamol overdoses. Patients were included if they had ingested a toxic dose (> 10 g) of MR paracetamol over a period of 8 hours or less. Of 116 patients recruited within a study period of 4.5 years, 113 (97%) were commenced on acetylcysteine. Serum paracetamol: 78 (67%) had a serum paracetamol level above the nomogram line at the initial measurement (≥ 4 hours), 6 patients had a double paracetamol peak of whom 3 were late line crossers and 2 developed hepatotoxicity. Outcomes: 21 (18%) patients developed hepatotoxicity, none required liver transplantation and none developed hepatic encephalopathy. The median paracetamol dose was 32 g, one fatality was reported but was not directly linked to the MR paracetamol ingestion (Chiew et al 2018).

The key finding from this literature is that the majority of patients recovered with or without treatment with acetylcysteine and none of the patients required a liver transplantation. Overall, the review of published literature articles suggests that the nature, severity of the events, and outcome in overdose experiences with MR and IR formulations of paracetamol are no different.

5.2.3 [GSK worldwide clinical safety database

5.2.3.1 Analysis of overdose cases

To further understand the context of MR paracetamol overdose, a search of the GSK worldwide clinical safety database was undertaken on 07 July 2017, using the following criteria:

- **Data lock point(s):** Cumulative to 06 July 2017
- **Report types:** All spontaneous reports, post-marketing surveillance reports, and unblinded serious clinical trial reports (attributable and non-attributable).
- All paracetamol single active product reported as a suspect drug, (MR paracetamol was determined using a list of trade names).
- **Countries:** All markets.
- **MedDRA Terms:** GSK's standard search strategy for overdose (Updated on 03 January 2017 to remove medication error terms due to the availability of a medication errors SMQ).

A total of 4662 cases of overdose associated with single active paracetamol have been retrieved from the GSK worldwide safety database cumulatively to 06 July 2017 (Figure 1, below). Of these, 319 cases were associated with overdose of paracetamol MR 665mg; based on review of the case details these included 184 cases of intentional overdose, 7 cases of unintentional overdose and 128 cases classified as unknown.]

A summary of the cases by source, age, gender, and country of origin (Table 2, below) demonstrates that the pattern of overdose associated with MR paracetamol is similar to IR paracetamol, based on the known demographics of intentional overdose patients (female, teenage/young adults) as defined in the paper Schmidt (Schmidt 2005).

Figure 1. Overview of case distribution

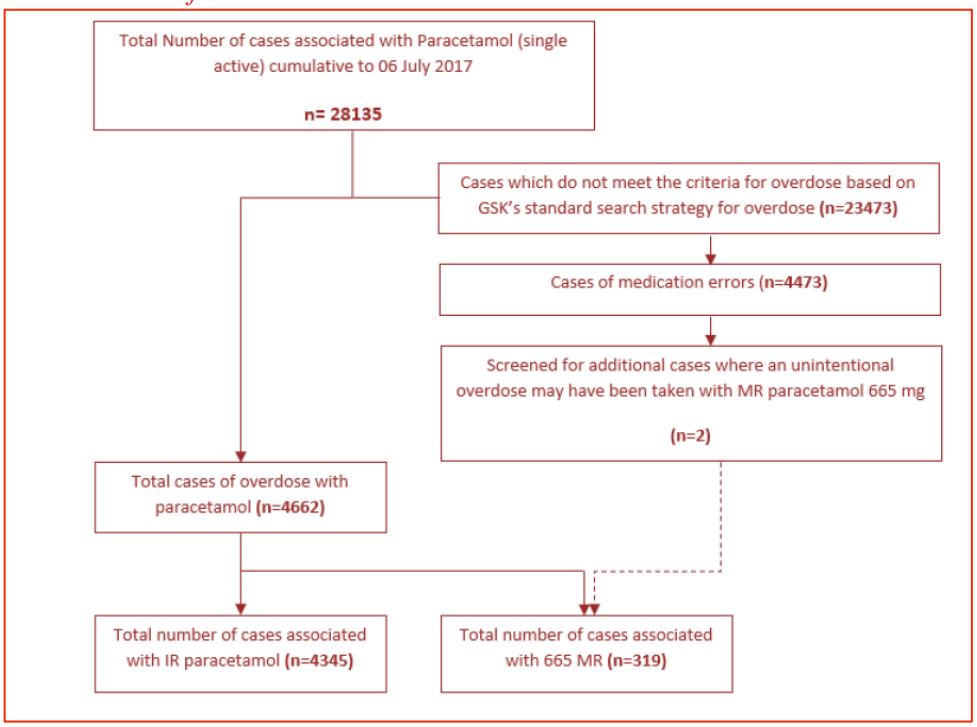


Table 2. Overview of overdose cases associated with paracetamol 665 mg modified release tablets: Intentional versus Unintentional (n= 319).

	Intentional (n=184)	Unintentional (n=7)	Unknown (n=128)
Source			
HCP	179	0	32
Non-HCP	5	7	96
Age (years)			
0-15	24	0	5
16-25	61	0	1
26-35	25	0	0
36-45	23	0	2
46-55	19	0	3
56-65	9	2	2
>65	12	3	6
Unknown	11	2	109
Gender			
Male	50	3	24
Female	132	4	33
Unknown	2	0	71
Country of origin			
Sweden	115	1	97
Australia	67	6	27
Other*	2	0	4

* Countries: USA (n=1, intentional), Hong Kong (n=1, unknown), Denmark (n=1, intentional; n=2, unknown), Republic of Korea (n=1, unknown)]

[Of the 319 case reports, 164 cases contained insufficient information for assessment and/or were inconsistent with the reported term. These were defined as follows: case review indicated the patient had not received an overdose, or an overdose could not be verified following case review and case contained no information on clinical course (n=10), patient received an overdose, with no reported adverse events and no serum paracetamol concentrations are provided (n=127), patient experienced a non-serious adverse event requiring no intervention (n=4) and very poorly-documented cases providing no details about the event (i.e., no time to onset, duration, or outcome) or otherwise clinically unevaluable cases due to inadequate documentation (n=23).

Of the remaining 155 cases, 150 were reported as intentional overdoses (148 of which were acute ingestions), whilst in 4 cases, reported doses were close to therapeutic thresholds and did not provide sufficient information to determine if these were intentional or unintentional overdoses; the remaining case was an unintentional overdose.

Dose and time to presentation was available in 134 cases of intentional overdoses (Table 3). This data indicates that hepatic injury may occur irrespective of time to presentation and is more pronounced with increasing dose, the overall outcome however indicates that these patients can be appropriately managed.

The overall amount of data however is limited for definitive conclusions to be determined. The majority of cases for which an outcome was available showed improvement or recovery (93 cases, 69%); in 38 cases (28%) the outcome was not reported. None of the cases of intentional overdose where dose and time to presentation was reported resulted in a liver transplant; 3 cases were fatal.]

Table 3. Overview of MR paracetamol intentional overdose cases by dose vs time to presentation for acute overdoses (n=134 cases)

Dose (g)	**<10 (n=6)**		**10<20 (n=48)**		**20<30 (n=27)**		**30+ (n=53)**	
Time to presentation	**<10h**	**>10h**	**<10h**	**>10h**	**<10h**	**>10h**	**<10h**	**>10h**
Gender								
Male	0	0	7	0	10	3	11	5
Female	5	1	31	10	11	3	32	4
Unknown	0	0	0	0	0	0	0	1
Age distribution								
0-15	1	0	6	5	1	2	1	0
16-25	4	0	15	4	12	2	9	2
26-35	0	0	6	1	2	0	11	2
36-45	0	0	5	0	3	0	6	2
46-55	0	1	4	0	1	0	8	2
56-65	0	0	2	0	1	0	3	0
>65	0	0	0	0	1	0	4	1
Unknown	0	0	0	0	0	2	1	1
Serious								
Yes	5	1	38	8	17	5	42	10
No	0	0	0	2	4	1	1	0
Treatments								
Acetylcysteine treatment	4	1	19	10	18	6	41	10
Yes	1	0	3	0	3	0	1	0
No	2	0	9	0	6	0	13	0
Activated charcoal	0	0	7	0	0	0	1	0
Unknown/ other								
Outcome								
Improved	0	0	19	2	9	0	19	3
Recovered	2	3	11	3	8	1	15	1
Unresolved	0	0	0	0	0	0	0	0
Liver transplant	0	0	0	0	0	0	0	0
Fatal	0	0	1	0	0	0	1	1
Unknown	3	1	7	5	4	5	8	5

Overall, the majority (213; 67%) of these 319 cases have been reported in Sweden. This is of relevance, given that Australia constitutes the highest proportion of GSK MR paracetamol sales globally (78%) and Sweden some 10%, yet the prevalence of overdose

is reportedly higher in Sweden.] Data in the most recent annual report from the Uppsala Monitoring Centre (the WHO Collaborating Centre for International Drug Monitoring) establishes that the frequency of individual case safety reports per million inhabitants is similar in Australia, New Zealand and Sweden, indicating that the country-specific disparities in MR paracetamol overdose figures are unlikely to be the result of a bias in reporting standards between these markets (Uppsala Monitoring Centre, 2017).

This data arguably provides some insight on the action taken by Sweden to raise the matter with the PRAC. However, as stated in the MARC report, the situation in New Zealand is different and there has been no suggestion of a clinical concern regarding MR paracetamol medicines in New Zealand.

5.2.3.2 Analysis of the management of MR paracetamol overdose cases in which hepatic toxicity has been reported

[The GSK worldwide clinical safety database was previously searched on 19 March 2017, to evaluate overdose cases in which hepatic toxicity was reported. A total of 803 cases of overdose associated with drug related hepatic disorders were retrieved, of which 753 were associated with the use of IR preparations of paracetamol, whilst 50 cases were associated with the use of MR paracetamol. All 50 cases relate to intentional acute ingestion of 665 mg MR paracetamol; 43 were from Sweden (all reported by the Regulatory Authority) and 7 were from Australia (from publications in the literature).

Of the 50 cases, 48 cases reported the amount of 665 mg MR paracetamol tablets ingested, which ranged from 8-166g. Of the 50 cases of 665 mg MR paracetamol reporting hepatic toxicity, 13 cases reported co-suspect medications. The majority of co-suspect medications were co-ingested and were for anxiety and depression (n=15) whilst the remaining co-suspect medications included non-steroidal anti-inflammatory drugs (n=5), montelukast (n=1) and cocillana (n=1; herbal medication for cough). There is no evidence in the literature that these medications in the context of overdose affect induction of CYP.

Alcohol use was reported in 8 cases, but in 3 cases, this was in the context of a medical history with no evidence that alcohol was co-ingested with 665 mg MR paracetamol. In 4 cases the amount of alcohol co-ingested was not reported. In 1 case (SE2016095166) the patient had consumed 75 cl spirits in addition to 53 g of 665 mg MR paracetamol. This patient presented to hospital 36-48 h post ingestion; he required extended treatment with acetylcysteine and recovered from the event.

In the 7 Australian cases the dose ingested was ≥10 g and therefore all patients received treatment with acetylcysteine. Of the 43 Swedish cases, 28 cases would have met the criteria for acetylcysteine treatment based on the 2016 revised Swedish treatment guidelines, and a further 14 presented to hospital <4 hours so would have received appropriate clinical care. In 1 case (SE2016094629) the patient was below the treatment line, however in this case treatment with acetylcysteine was provided.

Twenty-eight (28) of the cases were ‘late line crossers’ (defined as patients whose early serum paracetamol measurements were below the acetylcysteine treatment line but whose serum paracetamol later rose and crossed the treatment line). Of these, 14 cases relate to

hepatic toxicity and all 14 cases originated from Sweden. Late line crossing was determined using the Rumack-Matthew nomogram, however if the revised Swedish treatment guidelines are applied this is reduced to 6. Of the 6 patients who were late line crossers according to the Swedish treatment practice, acetylcysteine was provided in 4 instances; in the remaining 2 cases (SE2016095248/ SE2016095262) no acetylcysteine was provided as liver values remained normal. The patients were all reported to have survived.]

A review of the post-marketing data confirms the published data of Chiew et al, 2018 that delayed peaks of serum paracetamol drug levels could occur following overdose with MR paracetamol (Chiew et al 2018). Treating physicians should utilise existing paracetamol overdose management protocols as a guide. Chiew et al recommend that, due to a delay in peak paracetamol levels, multiple serum samples should be taken to guide appropriate management (Chiew et al 2018). If any liver injury is suspected, treatment with acetylcysteine should continue accordingly, or, if elevated levels of paracetamol continue, treatment with acetylcysteine should be maintained as clinically indicated, until confirmation that levels have peaked are declining and the patient is no longer at risk of ongoing hepatic injury. The benefits of prolonged acetylcysteine treatment outweigh any incremental risk.

The Australian and New Zealand paracetamol overdose guidelines have been established in New Zealand for over a decade. They combine an upper threshold (>10 g paracetamol) for the treatment of overdose with a single nomogram line for people with a suspected overdose below this toxic threshold. The above findings confirm that they mitigate risk of hepatoxicity from MR paracetamol overdose, as they do for IR paracetamol. This position is further strengthened with the data from the PK modelling study (see 5.1.1 above and Appendix 3) and the prior analysis showing that almost twice as many cases are appropriately managed when using an upper threshold for treatment of overdose rather than timed serum paracetamol concentration on a more conservative nomogram line (96.4% vs 57.8%; see section 3.1.4)

5.2.3.3 Australian (NSW) Poisons Information Centre data

A review of data provided by the NSW Poisons Information Centre indicated that from launch in 2001 up to March 2017 (16 years) there have been 81 cases of MR paracetamol overdose recorded. Of these 81 cases, 14 cases were considered ‘late line crossers’ and all had consumed >10 g of paracetamol and therefore, based on the Australian treatment practices, would have received treatment with acetylcysteine.

The information provided by NSW PIC did not include information on treatment or clinical course, however it should be noted in 77 cases the ingested dose exceeded 10 g. There were no deaths attributed to MR paracetamol overdose in the data provided.

5.2.4 Sponsor’s comment

Data from markets other than Sweden suggest that the Salmonson dataset is not typical of outcomes globally. The two published case series from Australia are of more relevance to

New Zealand because, unlike Sweden, these two countries share the same overdose guidelines and market MR paracetamol for the same indication (persistent pain associated with osteoarthritis).

Case series from Australia:

- Graudins 2014 reports on a series of 42 cases in which 27 were single acute ingestions and 4 (15%) of these cases had initial non-toxic plasma paracetamol concentrations. These patients required a repeat serum measurement. No patients developed acute liver failure and there were no fatalities (Graudins 2014).
- Chiew, 2018 reports on a series of 116 cases of acute toxic ingestions. Most patients (113; 97%), received acetylcysteine of whom 67 (59%) received prolonged treatment beyond the standard 21 hour period; 21 (18%) patients developed hepatotoxicity, none required liver transplantation and none developed hepatic encephalopathy. One fatality was reported but was not directly linked to the MR paracetamol ingestion (Chiew et al 2018).

[Australia is the sponsor's largest MR paracetamol market worldwide; based on IMS data Australia accounts for 78% of MR paracetamol tablet volume sales.] Case series from Australia demonstrate that patients with MR paracetamol overdose can be managed successfully according to the established guidelines.

6 New Zealand specific information

6.1 Centre for Adverse Reactions Monitoring (CARM) data

Medsafe Submission:

The New Zealand Pharmacovigilance Centre has identified one case of overdose in which modified-release paracetamol is possibly implicated.

6.1.1 GSK Safety Database

The information provided by Medsafe concurs with that in the GSK safety database. Further details pertaining to this one case are provided below. Of note, this case is excluded from the analyses of overdose cases (section 5.2.3.1) because it did not meet the criteria for an overdose based on pre-specified search terms.

This case (received from a consumer) described a serious event of 'Hepatic enzyme increased' in a 74-year old female patient who (on an unknown date in July 2008) commenced Panadol tablets for pain associated with osteoarthritis. The patient was taking the recommended dose of 2 tablets at 4 times per day, and it was reported that the patient had recently had two liver enzyme tests that had come back with high readings.

During this time, it was recommended that the patient should use Panadol Osteo in the morning and regular Panadol in the evening. In December 2008 the patient started Panadol Osteo (oral).

The patient had spoken to two doctors regarding the high readings: one suggested to just monitor and the other didn't seem to think that the amount of paracetamol the patient had been taking would cause the high readings. The patient also stated that she had another test done last and was still waiting for the result, and that she is also awaiting a hip operation. At the time of reporting, the event was unresolved. This case was assessed as medically serious by GSK.

6.1.2 Sponsor's comment

This is an isolated case, in which the dosing error appeared to stem from confusing off-label use advice. This single, non-serious reported case of excess use (5320 mg per day instead of 3990 mg) did not reach the threshold for overdose management requirement (10 g). Of note, the dose ingested in this case (8 tablets in a 24 hour period) is significantly lower than in the Swedish case reports, in which the median dose was reported to be 20 g (range 10-166 g; 15-250 tablets).

In the context of product use over a period of 10 years, this single case provides an insufficient basis upon which to make a scheduling classification change. Were such decision-making practice to be applied common-place to other products, it seems reasonable to conclude that very few medicines would be available as Pharmacy Only.

It is recognized that MR paracetamol provides benefits for osteoarthritis pain management (Ortiz et al 2016). The product is well known to the medical community as a first-line management option for mild to moderate osteoarthritis pain; its use is supported by Pharmacists and GPs. The suggestion that this single case could be representative of wider-spread dose confusion is speculative. It is counterintuitive to suggest that a patient who has purchased at a considerable premium a product on the basis of it delivering 8-hour pain relief and being dosed three-times a day might then forget the relevance of this dosing regimen. In the instance of this single recorded overdose case, it appears the confusion stemmed from poor advice, contrary to the labelled use directions, making it even less relevant to the proposal it purports to underpin.

6.2 New Zealand National Poisons Centre data

Medsafe Submission:

The Medsafe submission summarises data from the National Poisons Information Centre, concluding:

This data indicates that confusion about the dosing of modified-release paracetamol products may lead to inadvertent supratherapeutic dosing. Reclassification of modified-release paracetamol to 'restricted medicine' would ensure the involvement of a pharmacist in the sale of the product, and that the consumer received advice on how often to take the medicine.

6.2.1 National Poisons Centre data in perspective

The National Poisons Centre is the only emergency service providing information to the New Zealand public and healthcare professionals. The NPC estimates a yearly call rate of around 30,000.

MR paracetamol has been available in New Zealand since 2008, nearly 10 years. The MARC considered contact data from the NPC for the period 1 January 2008 to 8 October 2017 (Table 4). The MARC noted that, although the number of calls over the 10-year period regarding MR paracetamol comprised a small number of total calls concerning paracetamol (31/13,594; 0.22%), the majority of calls relating to MR paracetamol (24/31; 77.4%) were for therapeutic error. Comparing this with the lower proportion of calls classified as therapeutic error for IR paracetamol (2990/13563; 22.0%), the MARC considered that this may indicate that consumers should receive counselling and advice on the dosing regimen of MR paracetamol and recommended that the MCC give consideration to reclassifying MR paracetamol from pharmacy-only to (restricted medicine) pharmacist-only.

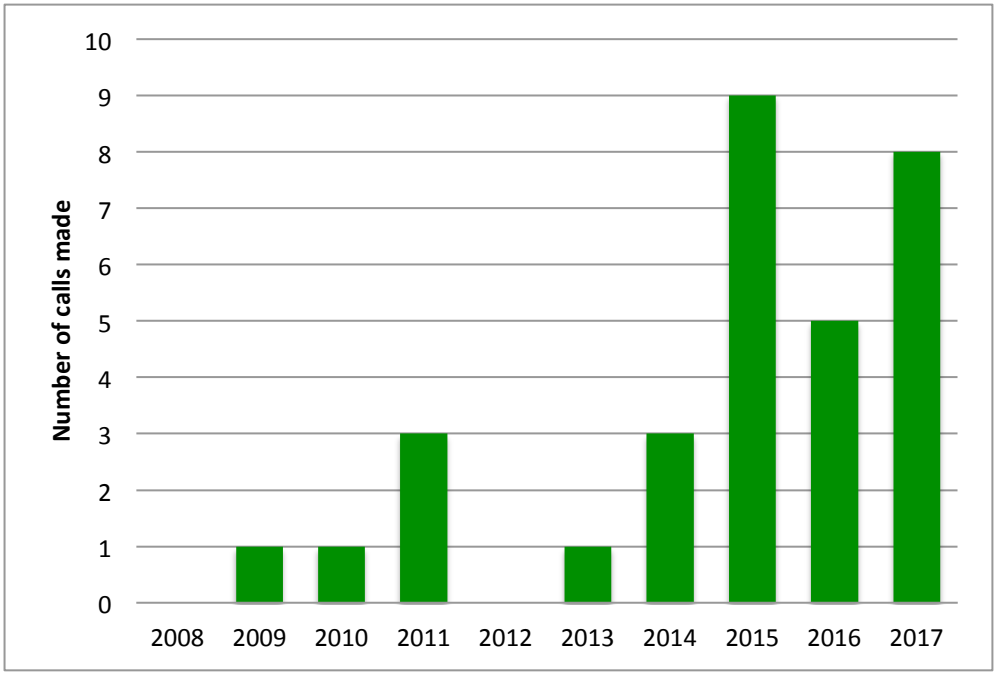
Table 4. Calls to the National Poisons Centre regarding IR paracetamol (n=13,563) and MR paracetamol (n=31) over 10 years

	IR Paracetamol		MR Paracetamol	
TOTAL CALLS	13,563		31	
Reason	n	%	n	%
Therapeutic error	**2990**	**21.9%**	**24**	**77.4%**
Child exploratory	5489	40.5%	3	9.7%
Intentional	2456	18.1%	2	6.5%
Unintentional	2392	17.6%	2	6.5%
Unknown	189	1.4%	0	0.0%
Abuse	47	0.3%	0	0.0%
Outcome	n	%	n	%
No treatment/reassured	7170	52.9%	23	74.2%
Medical referral (active investigation/treatment)	4219	31.1%	6	19.4%
Self-treatment	978	7.2%	1	3.2%
Medical referral (psych assess)	569	4.2%	0	0.0%
Further information required	388	2.9%	0	0.0%
Medical referral (unrelated)	241	1.8%	1	3.2%

The numerical trend in calls per year (Figure 2 below) roughly correlates with unit sales per year (Figure 3). However, the absolute number of calls regarding MR paracetamol is low reducing the ability to draw conclusions on the calls received. The timeframe within which these calls have been received reflects changes in the market. For example, the cluster of calls in 2009-2011 reflect the first few years after the launch of Panadol Osteo,

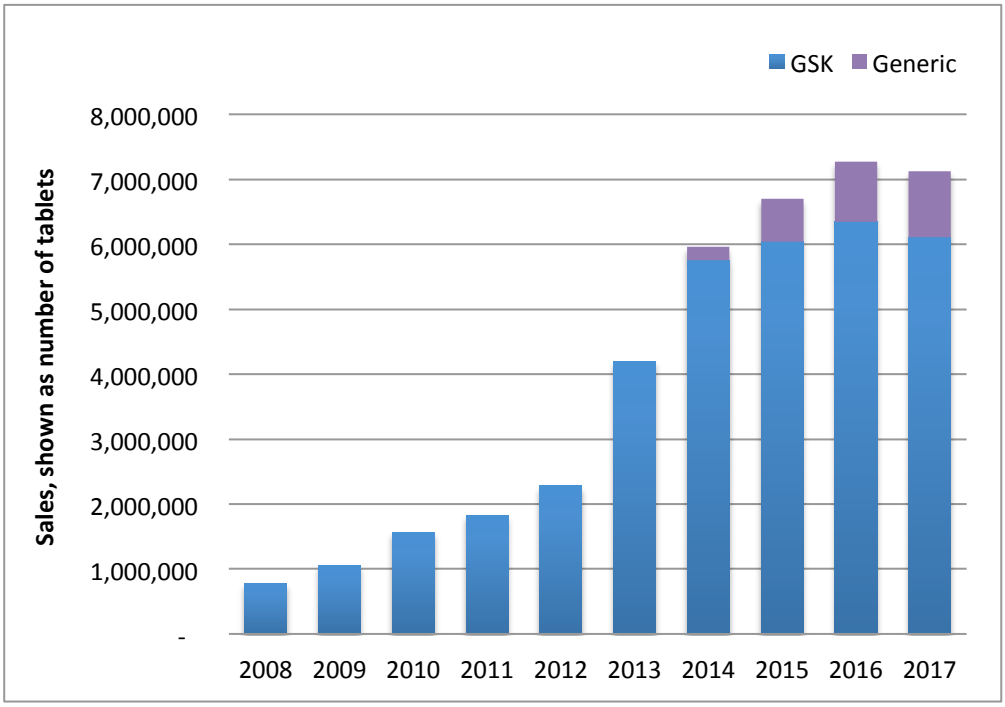
while the increase in calls in 2014-17 may reflect calls to clarify dosing with MR paracetamol after the introduction of a generic 665mg MR paracetamol product.

Figure 2. MR paracetamol 2008–2017: Annual number of calls made to the New Zealand National Poisons Centre



Data source: Correspondence with the New Zealand National Poisons Centre

Figure 3. MR paracetamol 2008–2017: Annual number of tablets sold



Data source: AZTEC NZ Pharmacy Scan data by tablet volume 2008-2017

As can be seen from the complete dataset (Table 4), the largest proportion of calls relating to IR paracetamol was for child exploratory. This might be reflective of the fact that child exploratory would be more common with the liquids (included in the IR category) which children could be likely to find more accessible and easier to take than MR tablets. In the period from 1 January 2008 and 10 August 2016, 13,594 calls were received by NPC for all paracetamol-containing products. Of the 31 calls regarding MR paracetamol over 10 years, 23 (74.1%) were not recommended to seek treatment. Only 6 patients were referred for medical investigation and/or treatment, as compared with 4,219 patients in relation to IR paracetamol calls.

GSKCH agrees that unintentional overdose presents a harder to manage scenario than does intentional overdose. Over the 10-year reporting period, there have been only 2 calls classified as unintentional in relation to MR paracetamol. Overall, the global dataset supports a low incidence of unintentional overdoses with MR paracetamol; 1 case in Sweden and 6 cases in Australia in the nearly 17 years since the product was first marketed globally by GSKCH (Table 2, section 5.2.3).

6.2.2 Sponsor's comment

Over the 10-year period that MR paracetamol has been available in New Zealand, there have been a total of 31 calls to made to the National Poisons Centre and 38,754,038 tablets sold (or one call for every 1.25 million tablets sold). This extremely low ratio of calls to tablets sold suggests a high confidence level in consumers of appropriate usage.

Risk mitigation measures, such as blister packaging and on-pack warnings, that have been in place since the product was first launched in 2008 and have since been further supported with ongoing consumer and healthcare professional educational campaigns. In addition, label warnings and dosing instructions (e.g. maximum six tablets in 24 hours, *doses should be equally spaced throughout the day; the caplets must not be crushed*) have been in place on the sponsor's MR paracetamol packs in New Zealand since 2008. Additionally, the packs include the instruction: "*If an overdose is taken or suspected, ring the Poisons Information Centre (AUST: 13 11 26; NZ: 0800 764 766) or go to the hospital immediately, even if you feel well because of the risk of delayed, serious liver damage if left untreated*." Furthermore, all Panadol packs include a free call 0800 telephone number on the pack whereby consumers can seek advice directly from GSKCH, any such calls made would be treated in line with our established adverse event procedures.

The most plausible explanation for the calls to the National Poisons Centre is that the majority of patients are using the product appropriately and that a small number of people with questions are following the on-pack guidance to call the New Zealand National Poisons Centre if they have any concerns. Irrespective of its scheduling status, it is highly likely that 2-3 people per annum would continue to seek other sources of information like the National Poisons Centre to clarify dosing questions after hours when the Pharmacist is unavailable.

Reclassifying MR paracetamol from its current pharmacy-only medicine status to restricted medicine is unlikely to negate the likelihood of consumers continuing to seek ad-hoc advice on its use in small numbers.

7 Discussion and conclusions

Medsafe Submission:

Modified-release paracetamol-containing products are being withdrawn from the European market following concerns about the complexity of managing overdose with these products.

Advice on the correct dosing by a pharmacist at the point-of-sale may help to reduce inadvertent supratherapeutic doses with modified-release paracetamol 665 mg tablets. Furthermore, introducing a healthcare provider step in the process of obtaining modified- release paracetamol may help to reduce the likelihood that this product is purchased with the intention to overdose (i.e. less chance of an impulse purchase, and an increased differential in the relative accessibility of immediate-release products).

Medsafe recommends that the MCC changes the classification of modified-release paracetamol 665 mg products to Pharmacist Only (restricted) medicine to ensure that consumers are advised of the correct dose of this medicine at the time of sale, thereby reducing the risk of inadvertent overdose. A restricted medicine classification may also reduce the ease of access, relative to immediate-release paracetamol, for intentional overdose, without limiting access to the product for its therapeutic purpose

7.1 Use of MR paracetamol in osteoarthritis is underpinned by a strong clinical rationale

After non-pharmacological approaches, the most common action taken to manage osteoarthritic pain is the use of medications. Paracetamol is recommended as a first-line pharmacological treatment in many international expert guidelines. The recommended maximum daily dose of paracetamol for effective pain relief is 4000 mg/day. For IR paracetamol, this equates to two 500 mg tablets every 4-6 hours (4 times daily).

Australia's National Prescribing Service reports that poor adherence to dosing schedules, particularly when prescribed "as needed manner" may lead patients to perceive that their treatment is ineffective (NPS 2006). As a result, the possibility that patients require additional or alternative analgesia is increased.

MR paracetamol formulations provide equivalent efficacy as immediate release paracetamol formulations, with the advantage of sustained analgesia over an 8-hour period to enable a reduction in the daily dose frequency to three doses per day (Bacon 2001, Bacon et al 2002).

The clinical rationale for using an MR paracetamol formulation is to provide a product with an 8-hour duration of action to facilitate adherence and improved outcomes. Given that joint pain is frequently a chronic complaint requiring long-term analgesic use, simplifying treatment regimens, improving patient convenience, adherence and improving overall quality of life and better health outcomes are key objectives that shape the way such conditions are managed and enables informed treatment decisions.

An Australian retrospective cohort longitudinal analysis has been conducted to compare usage patterns of 665 mg MR paracetamol tablets versus IR paracetamol in patients (n=74,115) with osteoarthritis over a 2-year period. Significantly more patients switched from IR to 665 mg paracetamol tablets than switched from 665 mg paracetamol tablets to IR paracetamol (13.2% vs 3.1%, $p<0.001$). Long-term continuous use, defined as "no gap in continuous therapy at 24 months", was higher amongst patients prescribed 665 mg paracetamol tablets than those prescribed IR paracetamol (26.1% [95% CI 24.5-26.8%] vs 11.9% [95% CI 10-8-13.1%, $p<0.001$]). Use of opioid combinations or stronger opioids was also higher ($p<0.001$) in those patients taking IR paracetamol, indicating that patients taking 665 mg paracetamol tablets were less likely to move up the analgesic pyramid. The explanation given by the authors is that patients experienced better analgesia with 665 mg paracetamol tablets dosed three-times daily than from the IR paracetamol. They also suggested that tablet burden and dose frequency were a barrier to appropriate use in patients who are prescribed IR paracetamol (Ortiz et al 2016).

In an Australian preference study evaluating the utility of 665 mg paracetamol tablets, 8 out of 10 patients with osteoarthritis reported that a three-times daily regimen would be easier to adhere to than a four-times daily regimen if paracetamol was to be taken regularly. The same study also found that 665 mg paracetamol tablets provided better overall joint pain relief and resulted in higher levels of satisfaction versus IR paracetamol (Benson et al 2009).

There are robust data to support the clinical rationale for MR paracetamol when used to manage mild to moderate pain associated with osteoarthritis and some, albeit limited, data to further support that these benefits translate into positive outcomes with regard to quality of life (Table 5, next page).

Table 5. Data supporting the benefits of using MR paracetamol instead of an IR formulation in the management of osteoarthritis

BENEFIT ATTRIBUTES [✓ indicates that available data supports these benefits and outcomes]	
Feature: Three times daily dosing	
Reduced pill burden	✓ **(Ortiz, 2016; Benson, 2009)**
Simplified dosing schedule	✓ **(Ortiz, 2016; Benson, 2009)**
Improved convenience	✓ **(Ortiz, 2016; Benson, 2009)**
Increased user preference	✓ **(Ortiz, 2016; Benson, 2009)**
Improved adherence	✓ **(Ortiz, 2016)**
Feature: Steady state serum concentration	
Better around-the-clock pain control	✓ **(Ortiz, 2016; Bacon, 2002)**
Better overnight pain control	**No published data**
Reduced incidence of breakthrough pain	✓ **(Ortiz, 2016; Bacon, 2002)**
Outcome: Rescue/Alternative analgesia	
Less likely to move up the analgesic ladder to narcotic analgesics	✓ **(Ortiz, 2016)**
Reduced burden of side effects from using opioids	✓ **(Ortiz, 2016)**
Less likely to move up the analgesic ladder to NSAID analgesics	**No published data**
Reduced burden of side effects from using NSAIDs	✓ (Ortiz, 2016)
Outcome: Impact on quality of life	
Increased number of consumers successfully managing their pain	✓ **(Ortiz, 2016)**
Improved activities of daily living	**No published data**
Improved sleep quality	**No published data**
Reduced overall cost of care	**No published data**

7.2 MR paracetamol: Benefit-risk profile when supplied as a pharmacy-only medicine

The MCC advises that a benefit-risk assessment be undertaken when making a rescheduling application ("*Before making an application for reclassification Applicants are encouraged to make a benefit-risk assessment of the medicine, proposed for reclassification, before making an application to the MCC*" (Ministry of Health 2014). This is usually carried out to account for wider public access when down-scheduling a medicine. In this instance we are addressing the need for a proposed up-scheduling that will restrict consumer access to MR paracetamol. As such, a benefit-risk assessment

remains relevant and has been undertaken to establish the continued appropriateness of supplying MR paracetamol as a pharmacy-only medicine in New Zealand.

The MCC seeks to determine whether it is appropriate to reclassify MR paracetamol from a pharmacy-only medicine to a restricted medicine.* In this context, the primary differentiators between these two schedules are (1) the need for intervention by a registered pharmacist, (2) the need to record the sale and (3) for that sale to have taken place in a pharmacy.

To answer this question, a benefit-risk assessment (Table 6, following pages) has been undertaken that explores the appropriateness of MR paracetamol when made available to consumers as a pharmacy-only medicine and whether there is any compelling evidence, in the local market, to suggest that restricting access would further enhance that position.

The outcome of this analysis suggests that a more restrictive access to MR paracetamol would be unlikely to improve on the safety record of this product in New Zealand.

The only scenario where it could be suggested that some additional benefit might be conferred from mandatory pharmacist advice on dosing prior to dispensing is when a first-time user purchases the product. However, it is counterintuitive to suggest that a patient who has self-selected the MR paracetamol product at a considerable price premium (on the basis of it delivering longer (8-hour) pain relief and less frequent dosing (three-times a day versus four) might then forget the relevance of this dosing regimen. Therefore, it is unlikely, that reclassification to restricted medicine would have a substantial enough benefit to out-weigh the down-sides of more restrictive access to the overwhelming majority of customers who use the product safely.

As is suggested in the literature (e.g. Chiew 2018) and from the GSKCH PK modelling (Appendix 3), refinements to the overdose guidelines may further enhance their utility in managing MR paracetamol overdose cases. However, overdose management will proceed per guidelines irrespective of how the consumer accessed the medicine, so such changes have little bearing on the scheduling of MR paracetamol.

* Definitions:

- **Restricted medicine** (also referred to as pharmacist only medicine) – restricted medicines may be sold without a prescription, but the sale must be made by a registered pharmacist, in a pharmacy, and details of the sale must be recorded.
- **Pharmacy-only medicine** (also referred to as pharmacy medicine) – pharmacy- only medicines may only be sold in a community or hospital pharmacy, or a shop in an isolated area that is licensed to sell that particular medicine. The sale may be made by any salesperson.

Table 6. Benefit-risk assessment on the appropriateness of MR paracetamol scheduling in New Zealand.

Benefit & Risk Considerations	Pharmacy-Only Medicine	Restricted Medicine
	Rationale	**Rationale**
Benefits		
Consumer access	In the 10 years that MR paracetamol has been available in New Zealand, there has been one call made to the Poisons Information Centre for every 1,197,032 tablets sold. This extremely low ratio of calls to tablets sold suggests with a high level of confidence that consumers are able to use the medicine appropriately.	More restricted access is unlikely to substantially alter this number of calls. More restricted access may result in consumers reverting to using IR paracetamol, or NSAIDs.
Clinical outcomes	MR paracetamol is well known to the medical community; Pharmacists and GPs support its use in this setting. MR paracetamol is a useful treatment for patients who are unable to take non-steroidal anti-inflammatory drugs due to tolerability or contraindications, without the need to adhere to the four-times daily dosing schedule required with IR paracetamol.	If more consumers revert to using IR paracetamol, clinical outcomes may be reduced as was demonstrated in the 2016 Australian study (Ortiz et al 2016).
Public health	No data to suggest that there is a public health issue with availability of MR paracetamol in this schedule. As expressed by the MARC, there has been no suggestion of a clinical concern regarding MR paracetamol medicines in New Zealand.	No public health issues have been identified that might be improved with more restrictive access to MR paracetamol.
Consumer	Risk mitigation measures, such as blister	For first time purchasers:

involvement	packaging, clear labelling and on-pack warnings, have been in place since MR paracetamol was first launched in 2008. For first time purchasers: Labelled instructions make it clear that the product should be dosed three times daily. Purchasers pay a premium to access the benefit of longer duration of action and convenience of 3 times daily dosing. For repeat purchasers: Will be familiar with the medicine and its three-times daily dosing schedule.	There is a perceived benefit to mandatory pharmacist advice to ensure the consumer is aware of dosing. For repeat purchasers: Unlikely to add value as already familiar with the medicine, but may add a barrier to accessing this medication.
Economic benefits	Economic benefit is unaffected as the costs of MR paracetamol are the same if no change to classification occurs.	Economic benefit is potentially affected as the costs of mandatory pharmacist advice/dispensing with have an associated cost reflected in the purchase price to patients.
Risks		
Unintended misuse/overdose	Over the 10-year period that MR paracetamol has been available in New Zealand, the New Zealand Pharmacovigilance Centre has identified only one (1) case of overdose (non-serious) in which this product was possibly implicated and there have been 31 calls to the National Poisons Information Centre in relation to MR paracetamol. There are only two (2) recorded calls relating to unintentional misuse with this medicine.	The available data support an established level of safety and very low level of unintended misuse/overdose, more restricted access is unlikely to be able to improve on this proven track record.
Intentional misuse/overdose	Over the 10-year period that MR paracetamol has been available in New Zealand, there are	The available data support an established level of safety and very low level of intended

	only two (2) recorded calls relating to intentional misuse with this medicine.	misuse/overdose, more restricted access is unlikely to be able to improve on this proven track record.
Accidental ingestion	Over the 10-year period that MR paracetamol has been available in New Zealand, there are only three (3) recorded calls relating to child exploratory concerns with this medicine.	The available data support an established level of safety and very low level of accidental misuse by minors, more restricted access is unlikely to be able to improve on this proven track record.
Worsened outcome	Of the 31 calls regarding MR paracetamol over 10 years, 23 (74.1%) were not recommended to seek treatment. Only 6 patients were referred for medical investigation and/or treatment.	The available data support an established level of safety more restricted access is unlikely to be able to improve on this proven track record.
Overdose management	The Australian and New Zealand overdose guidelines state that antidote treatment (with acetylcysteine) should be in all patients with an ingested dose >10 g (Chiew et al 2015). Overdose management guidelines are established and data from Dunedin demonstrates that they are being used in New Zealand (Fountain et al 2014). Recently published Australian data show that 113/116 (97%) patients with acute MR overdose received acetylcysteine, 21 (18%) patients developed hepatotoxicity, none of these patients required a liver transplant or hepatic encephalopathy, and all survived. The management of MR paracetamol overdose in Sweden is very different to that in New Zealand. Current data do not suggest an inadequacy of the current Australian and New Zealand guidelines. Additional modifications, to encompass multiple	The majority of overdose cases reported in the GSK safety database were from Sweden, eventhough access to MR paracetamol was more restricted (prescription only). Overdose management will proceed per guidelines irrespective of how the consumer accessed the medicine.

	sampling and an extended period for monitoring appear to be warranted and should be investigated further but do not impact the scheduling status of this medicine.

7.3 Key differences in the misuse of paracetamol in Sweden contribute to its safety in use in New Zealand

The situation in Sweden is different to that in New Zealand. The MARC review commented that the classification, marketing and funding of MR paracetamol products in Sweden had meant that their availability for use as agents for overdose were considerably higher in Sweden than is currently the case in New Zealand. Key differences between the MR paracetamol products in New Zealand and Sweden are summarised in Table 7.

Table 7. Contributors to the differences in availability of MR paracetamol as a potential agent to be used in overdose: Sweden versus New Zealand

	New Zealand	**Sweden**
Classification	Pharmacy Only	Prescription
Cost of supply	Consumer pays, no subsidies and not available via PHARMAC	Funded prescription medicines are free of charge to the consumer once they have met the annual threshold for out-of-pocket expenditure on prescription items*
Labelled indications	Persistent pain associated with osteoarthritis.	Acute and chronic pain states, including headache, period pain, toothache, symptoms associated with cold and flu, fever, muscle and joint pain, pain associated with osteoarthritis
Total paracetamol calls to PIC	13,594 over 10 years*	4391 (in 2016)*
MR paracetamol calls as a percentage of total paracetamol calls to poisons centres	0.22% (31/13954)*	21%*

* Data sourced from MARC review report – 7 December 2017

This information clearly shows that there is a different pattern of misuse of MR paracetamol in Sweden leading to a higher burden of overdose than there is in New Zealand, despite the product being available self-select to consumers inside Pharmacies in New Zealand.

7.4 Information, education and training available for Panadol Osteo (MR paracetamol)

The appropriate use of MR paracetamol for the management of mild to moderate pain associated with osteoarthritis in the self-select environment (e.g. pharmacy-only medicine) is further supported by a variety of information, education and training materials. These materials, described below, provide consumers and healthcare professionals with multiple avenues through which to access information to ensure the safety in use of this MR paracetamol product. The primary product benefits – its longer (8-hour) duration of action and three-times daily dosing – are a consistently prominent feature in all of these materials. The up-take of the educational messages conveyed in these materials by consumers in New Zealand is established based on the very low number of calls to the National Poisons Centre regarding the use of MR paracetamol medicines in New Zealand.

7.4.1 Consumer information and education

7.4.1.1 Product Labelling

7.4.1.1.1 Product carton (pack)

GSKCH is committed to patient safety and produces clear, consumer-oriented packaging and labelling. The outer carton of Panadol Osteo (665mg MR paracetamol) carries the core claim of up to 8-hour pain relief on the front and back of the pack. In addition, clear dosage instructions (based on performance- based labelling principles for which GSKCH has previously been awarded best practice) establish the parameters for product use:

- Two tablet dose
- 8 hour pain relief
- Maximum 6 tablets in 24 hours

Front of pack

Back of pack and end flap

PANADOL OSTEO is a bi-layer formulation that has an immediate and a sustained-release layer of paracetamol, providing long-lasting pain relief for up to 8 hours.

USE PANADOL OSTEO FOR

Panadol Osteo is effective for the relief of persistent pain associated with Osteoarthritis. Suitable for:

- People with stomach ulcers
- Breastfeeding mothers

DO NOT USE PANADOL OSTEO

- If you are allergic to paracetamol
- More frequently than every 6 hours
- If using any other medicines containing paracetamol
- For children below age 12
- For more than 48 hours for children aged 12-17 except on medical advice
- For more than a few days at a time in adults except on medical advice
- If any of the seals on this packaging are broken
- If the packaging use-by date has expired
- Until you have read the enclosed leaflet carefully

CHECK WITH YOUR DOCTOR BEFORE USING IF YOU

- Have liver or kidney problems
- Are taking warfarin (a medicine used to thin the blood)

HOW TO USE PANADOL OSTEO

Age	Caplets	How often
12- Adult	2	Swallowed whole with water three times a day every 6 - 8 hrs (maximum 6 caplets in 24 hrs)

- Doses should be equally spaced throughout the day
- Can be taken with or without food
- The caplets must not be crushed

Store below 30°C.

STOP USE AND TELL YOUR DOCTOR IF YOU

Have an allergic reaction, shortness of breath or wheezing after taking Panadol.

EACH CAPLET CONTAINS

• 665mg Paracetamol • No gluten, lactose or sugar

KEEP TO THE RECOMMENDED DOSAGE

If an overdose is taken or suspected, ring the Poisons Information Centre (Australia 131 126: NZ 0800 764 766) or go to the hospital immediately even if you feel well because of the risk of delayed, serious liver damage if left untreated.

As evidenced above the Panadol Osteo pack, as is the case with all Panadol packs, carry details of a Panadol NZ web-site which in this instance is www.myosteolife.co.nz.

This website includes both a product page and frequently asked questions section that gives prominence to the 8-hour duration of action, the three times daily dosing of Panadol Osteo and differences between IR paracetamol versus MR paracetamol (see below screenshots).

WHY PANADOL OSTEO?

Osteoarthritis tends to be a persistent condition - something that, if not managed properly, may impact your day-to-day life significantly. Alongside holistic treatment plans, Paracetamol is a trusted medication that can be used in a wide range of people, including infants and breastfeeding mothers.

Chances are, you have used Paracetamol to relieve headache or the symptoms of colds and flu. Using Paracetamol to relieve the pain and stiffness of Osteoarthritis is slightly different.

Panadol Osteo contains a higher dose of Paracetamol than regular Paracetamol tablets and, with just 3 times a day dosage, may provide up to 24-hour relief from pain.

Panadol Osteo brings you a unique bi-layer tablet that is gentle on the stomach. One layer delivers fast release, while the other provides long lasting pain relief for up to 8 hours*. So you can have the freedom to do more.

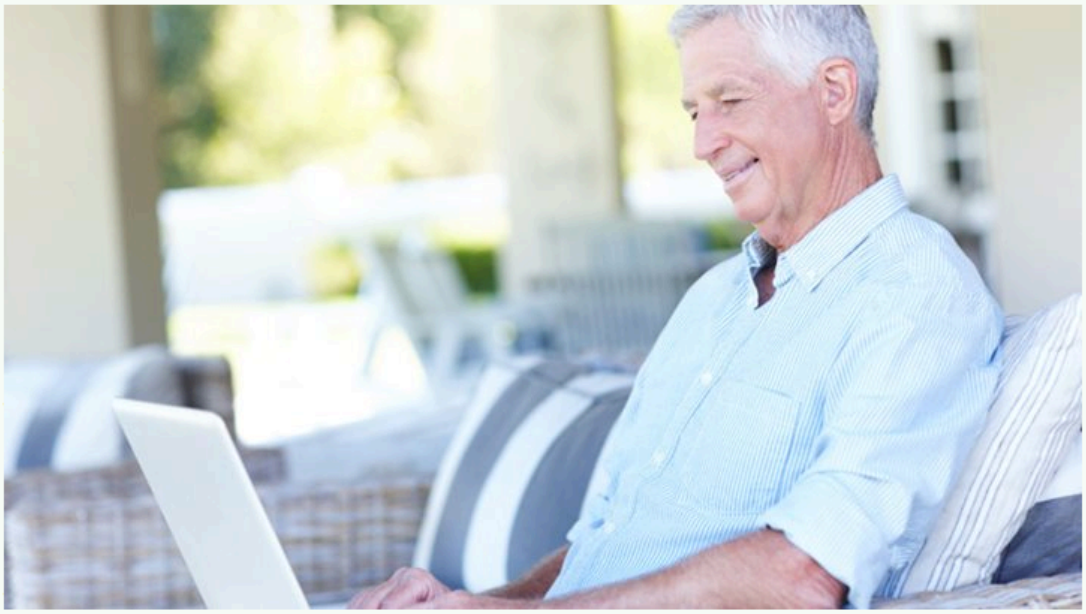
The Paracetamol is released in 2 stages
1. 31% of the Paracetamol in Panadol Osteo is released immediately, for rapid onset of action.
2. 69% of the Paracetamol in Panadol Osteo is released slowly, to provide prolonged pain relief, for up to 8 hours.

Dosage

Regular paracetamol	Panadol Osteo
500 mg paracetamol per tablet (immediate release)	665 mg paracetamol per tablet (modified release)
2 tablets may provide up to 6 hours pain relief	2 tablets may provide up to 8 hours pain relief
Maximum 8 tablets in 24 hours	Maximum 6 tablets in 24 hours

*when used as directed taking 2 tablets

FAQS



What is Panadol Osteo?
What is Panadol Osteo used for?
Where can I obtain Panadol Osteo?
Can I buy Panadol Osteo without a prescription?
How does Panadol Osteo compare to Panadol 500mg?
Can I take Panadol Osteo during pregnancy?
Can I take Panadol Osteo when breastfeeding?
Does Panadol Osteo contain gluten?
Does Panadol Osteo contain codeine?
Is there any sodium in Panadol Osteo?
What is the recommended dose?
Can I crush the caplets?
Do I take Panadol Osteo with or without food?
Can you use the product after the expiry date?

How does Panadol Osteo compare to Panadol 500mg?

Panadol Osteo and immediate release Panadol at recommended doses deliver clinically equivalent levels of paracetamol. Panadol Osteo is designed to maintain rather than increase plasma paracetamol concentrations compared to immediate release preparations.

The differences are:

- *Panadol Osteo provides more consistent levels of paracetamol due to the sustained release bi-layer (2 layers).*
- *A single dose of Panadol Osteo has longer lasting pain relief than a single dose of immediate release paracetamol.*
- *Panadol Osteo has more convenient dosing – Panadol Osteo is dosed 3 times daily and immediate release paracetamol is dosed 4 times daily.*

7.4.1.1.2 Package leaflet

Since 2017, GSKCH has been introducing product leaflets to all of its Panadol products in New Zealand (as part of a harmonised pack shared with Australia). As a result, Panadol Osteo is shipped with a product leaflet (CMI), which provides detailed dosing information as per the pack and the website.

The CMI and the corresponding Data Sheet are both also available on the Medsafe website. A CMI and Data Sheet are not mandatory for Pharmacy-Only Medicines. However, globally, GSKCH has a long-standing ethic of working to a high level of consumer safety standards and has made these items available to consumers, Pharmacists and Doctors to support the responsible, safe and effective use of its products.

The GSK NZ corporate website also carries links to the Panadol website and to the Consumer Medicine Information (CMI) for both regular Panadol tablets and Panadol Osteo directly from the Medsafe website CMI database:

http://nz.gsk.com/en-nz/products/our-consumer-healthcare-products/

http://www.medsafe.govt.nz/Consumers/CMI/p/panadoltab.pdf

http://www.medsafe.govt.nz/Consumers/CMI/p/panadolOsteo.pdf

7.4.1.1.3 Other online sources of Panadol Osteo specific product information available to consumers

Apart from the Panadol Osteo specific website, GSKCH also maintains the website (www.panadol.co.nz). Within this website there is an individual product page which provides details on the use of Panadol Osteo: https://www.panadol.co.nz/find-your-panadol/panadol-osteo-caplets.html?type=arthritis

This product information page speaks explicitly to:

- 8 hours pain relief
- Only 3 doses required to provide 24 of pain relief
- Maximum 6 tablets in 24 hours

[For 2018, GSKCH plans to introduce a revised consumer-facing website in New Zealand. The website – called "Osteoactive" – has recently been launched in Australia. It contains a product page that gives prominence to the 8-hour duration of action and the three times daily dosing of Panadol Osteo.

https://www.osteoactive.com.au/our-products/panadol.html]

7.4.1.2 Mainstream Media Advertising to consumers

[GSK has not advertised Panadol Osteo to consumers via mainstream media (TV, print) to date. However, was GSKCH to do so going forward, an example of a TV advertisement screenshot, which supports the 8-hour duration of pain relief and the three-times daily dosing which differentiate MR paracetamol from IR paracetamol, is provided.

Figure 4. Example screenshot from Panadol Osteo (665mg MR paracetamol) television advertisement, highlighting the duration of action and three-times daily dosing frequency

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7.4.2 Pharmacy information and education

7.4.2.1 New Zealand Panadol Osteo Training to Pharmacies

[Training and appropriate, safe usage and recommendation of GSKCH products is paramount. At GSKCH we employ a pharmacy specific sales force of five territory managers (TMs). GSKCH hosts Sales Force Cycle meetings four times a year with all GSKCH territory managers across the business. This is a mandated attendance forum to discuss upcoming sales and marketing objectives as well as providing product training for TMs with a focus on safe and appropriate use of Panadol Osteo. These meetings service as a forum to discuss safety data. In 2017 alone, two of these four meetings included training on Panadol Osteo:

- June 2017 - Refresher training on Osteo arthritis and Panadol Osteo
- March 2017 - Osteoarthritis training including a Panadol Osteo refresher (as part of the launch of Voltaren 12-Hourly 2% topical diclofenac topical gel).

Once trained, the territory managers then carry out in Pharmacy training within their territory. This is either as part of their booked pharmacy visits (if time permits) or a separate training is booked with the pharmacy team including Pharmacists.

Last year the GSKCH sales representatives carried out approximately 7 training sessions per week at Pharmacy level. The target audience comprised a combination of Pharmacists and Pharmacy Assistants. The total Pharmacy training sessions undertaken for Panadol Osteo last year was about 500 resulting in ~2000 pharmacy staff being trained per calendar year.]

7.4.2.2 Osteoarthritis online training initiatives for NZ Pharmacies

[In addition to the above GSKCH-led training sessions, the GSKCH Expert team also collaborates with healthcare professional organisations to deliver education and training materials. The GSKCH Expert team manages healthcare professional education, accredited learning (e.g. CPD modules), field sales training, and healthcare professional communication at congresses/conferences.

For example, the GSKCH expert team collaborated with Green Cross Health (who represent more than 350 of the 900 community Pharmacies throughout New Zealand) to develop additional training materials. As part of this, an osteoarthritis training module was made available on the Green Cross Health training academy, "Teach Me".

More than 5,500 Green Cross Health team members are enrolled in this Green Cross Health training academy (which has recently won global awards for its blended on and offline learning approach). Teach Me provides an opportunity for all Pharmacy Assistants to access the training and upskill their knowledge of osteoarthritis and of GSKCH products including Panadol Osteo. Green Cross Health encourage all Pharmacies within the group to complete the online modules and take the assessment quiz at the end. This training focuses on appropriate product recommendation highlighted by a safe and responsible approach to managing pain.

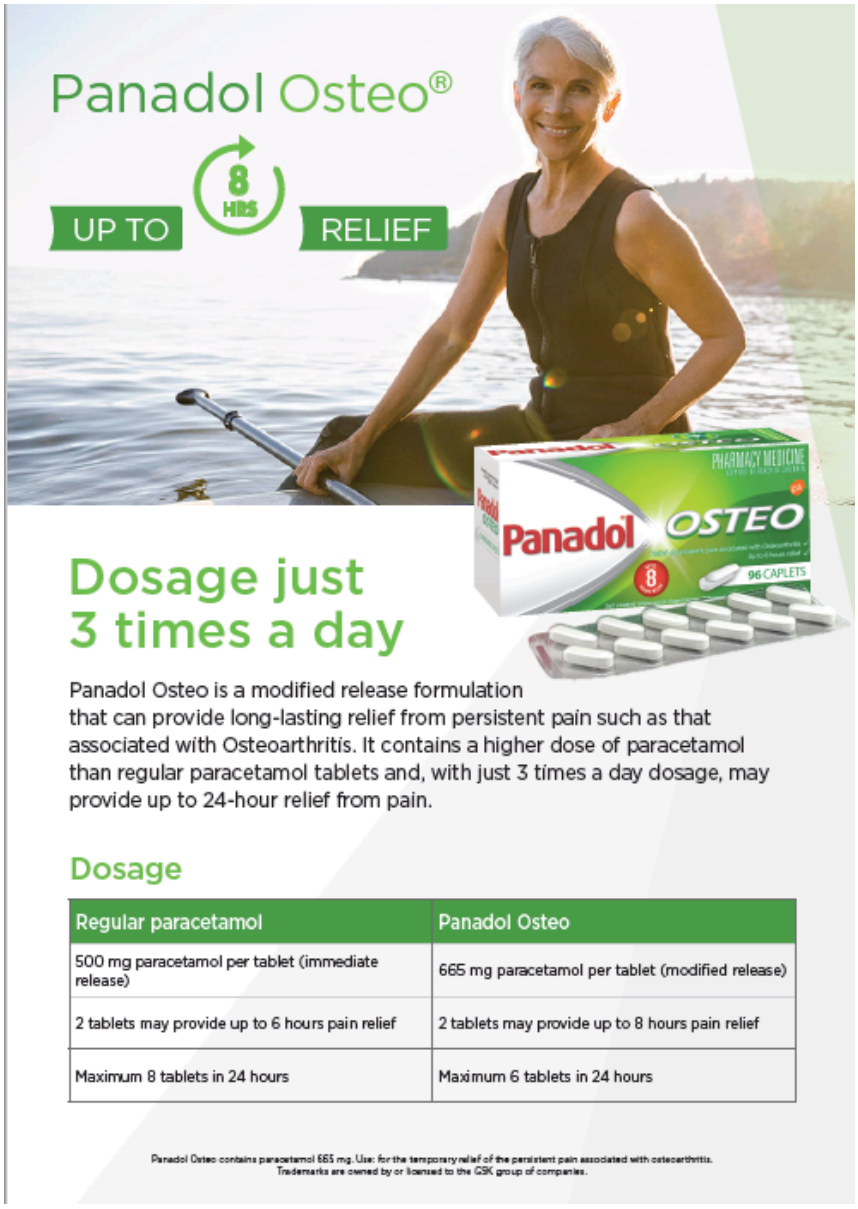
The current level of education and training of pharmacy teams would indicate the appropriate messaging is being given to consumers effectively, and this is further demonstrated by the small number of calls to seek information on appropriate usage of MR paracetamol over a 10 year period.

Nevertheless, GSKCH is also supportive of making this training readily available through the Pharmaceutical Society of New Zealand and/or other professional bodies in support of responsible, safe and appropriate self-selection and use of MR paracetamol by consumers.]

7.4.2.3 Panadol Osteo print based advertising for healthcare professionals

[Promotion of Panadol Osteo to health care professionals is underpinned by core messages that are supported by the product's strong clinical rationale (three-times daily dosing) and established favourable risk-benefit profile when used to manage pain associated with persistent conditions such as osteoarthritis. An example of the type of

promotional advertising designed to educate healthcare professionals on the core benefits of Panadol Osteo is provided below.



]

Based on the above, there is an extensive and established programme (both in prominence and frequency) of consumer information and training for pharmacists and pharmacy staff. When purchasing MR paracetamol, pharmacy staff is routinely trained and available to address consumers' questions, so as to address concerns and negate any need to reclassify MR paracetamol from pharmacy-only medicine to restricted medicine.

7.5 Actions undertaken in response to MARC review

The MARC review minutes were published in December 2017. The purpose of the review was three-fold:

- review the risks associated with overdose of modified-release paracetamol,
- examine the information currently available on the management of overdose with modified-release paracetamol formulations and consider whether the information currently provided in the data sheet is sufficient and consistent with current Australasian guidelines, and
- consider whether any further regulatory action is required in New Zealand, in light of the recent PRAC recommendation to suspend MR paracetamol from the EU market.

A detailed report can be found at: www.medsafe.govt.nz/committees/MARC/Reports.asp. The minutes from the MARC meeting presented a series of recommendations. A number of these recommendations have already been addressed and or undertaken by GSKCH, as summarised in Table 8.

Table 8. MARC recommendations and actions taken by GSKCH

MARC Recommendation	Actions taken or proposed
The Committee recommended Medsafe requests sponsor(s) of modified-release paracetamol products update the overdose section of their data sheets.	Completed. Data Sheet updated (21 February 2018)
The Committee recommended the Medicines Classification Committee considers reclassifying modified-release paracetamol from pharmacy-only medicines to pharmacist-only medicines.	Currently under consideration and the subject matter of this response
The Committee recommended Medsafe communicates with the National Poisons Information Centre to inform them of the Committee's discussion on this topic.	Not applicable for GSKCH
The Committee recommended communication with authors of the guidelines on the management of paracetamol poisoning in Australia and New Zealand to inform them of the Committee's discussion on this topic.	As noted in Section 5.1.2, GSKCH is in favour of amendments to the existing Australian and New Zealand overdose guidelines, to include multiple sampling and an extended period for monitoring. As an extensive supporter of this initiative for over two decades, GSKCH would welcome the opportunity to share the findings from its modelling and simulation exercise (Appendix 3) with the guideline authors.

The Committee recommended Medsafe includes an article on this topic in a future edition of Prescriber Update.	GSKCH would welcome this initiative and is happy to provide support via the provision of data and existing training materials if required.
The Committee recommended Medsafe requests Periodic Benefit Risk Evaluation Reports from the sponsor(s) of modified-release paracetamol products. This report should include worldwide usage data and New Zealand usage data	GSKCK provided the Periodic Benefit Risk Evaluation Reports as part of its response to Medsafe on 21 February 2018.

8 Sponsor's overall conclusion

It is reasonable to review the MR paracetamol classification in New Zealand in light of the recent EU decision. This decision arose from a concern by one member state which five of the other seven member states in which this product was marketed did not support.

The differences in New Zealand compared to Sweden and the EU are important, and indicate that the concern in Sweden is not repeated in New Zealand. There has been no suggestion of a clinical concern regarding overdose cases or the management of overdose with MR paracetamol medicines in New Zealand. During the 10-year period that MR paracetamol has been available, the New Zealand Pharmacovigilance Centre has identified one case of overdose (non-serious) in which this product was possibly implicated and there have been 31 calls to the National Poisons Centre in relation to MR paracetamol.

The licensed indication for MR paracetamol in New Zealand is "Relief of persistent pain associated with osteoarthritis". These products are supplied in packs containing 96 tablets. MR paracetamol has an overall acceptable benefit-risk profile when used to manage mild to moderate pain associated with osteoarthritis in a self-select pharmacy environment (pharmacy-only medicine). This medicine is well known to the medical community, where its use in this setting is supported by Pharmacists and GPs.

MR paracetamol is used for the management of a persistent pain condition. New users will either:

- have been recently diagnosed with osteoarthritis and recommended the product by their GP and are purchasing it in an environment where they have access to professional advice, or
- Self-select the medicine based on its price premium and positioning (8-hour duration of action and convenience of three-times daily dosing)

Repeat users will, by default, already be familiar with the medicine and its dosing schedule. Thus, for the majority of users, a more restrictive scheduling is unlikely to add value, but may add a barrier to accessing this medication. This may lead them to revert to

using IR paracetamol, which may lead to increased use of other analgesics as was demonstrated in an Australian study (Ortiz et al 2016).

Risk mitigation measures, such as blister packaging and on-pack warnings, have been in place since the product was first launched in 2008 and these are further supported with consumer and healthcare professional educational campaigns.

The management of MR paracetamol overdose in Sweden is very different to that in New Zealand. The current Australian and New Zealand guidelines for the treatment of MR paracetamol overdose are supported by an extensive documented clinical experience. Additional modifications, to encompass multiple sampling and an extended period for monitoring appear to be warranted and should be investigated further but do not impact the scheduling status of this medicine.

A change in classification of MR paracetamol will impact access for legitimate users while placing an unnecessary burden on pharmacists. The foreseeable net outcome would be one of a reduction in the quality use of medicines whereby patients with persistent osteoarthritis pain would revert to taking IR paracetamol and miss out on the benefits of this valuable option to reduce their pill burden.

In summary:

The MARC has identified two core themes upon which this consideration of the up-scheduling of MR paracetamol is being based. Firstly, the complexity of overdose management with MR paracetamol formulations and secondly concerns around the adequacy of consumer understanding that the dosing with this medicine is different to that with IR paracetamol.

The management of overdose with MR paracetamol is more complex than that with IR paracetamol. However, local guideline have been established and there are no grounds to suppose that emergency rooms in New Zealand might not be aware of MR paracetamol products or that they might not know how to manage overdoses cases with this medicine, should they occur.

The dosing of MR paracetamol is different to that with IR paracetamol. However, risk mitigation measures are in place and there are no grounds to suppose that patients are confused about its three-times daily dosing regimen and need direct Pharmacist intervention on every occasion of a purchase of this medicine.

GSKCH therefore submits that retaining MR paracetamol as a pharmacy-only medicine in New Zealand is justified.

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Uppsala Monitoring Centre: Annual Report 2017-2017.

10 Appendices

10.1 Appendix 1: Paracetamol Overdose Guidelines: Australia ad New Zealand

Guidelines for the management of paracetamol overdose

For Poisons Information Call
Australia 131 126
New Zealand 0800 764 766

General Information

1. Paracetamol overdose is a significant cause of hospital admission, but severe liver injury is rare and even when it does occur the prognosis is usually good.[1]
2. Signs consistent with paracetamol poisoning include repeated vomiting, abdominal tenderness in the right upper quadrant or mental status changes.[2]
3. Any patient should be considered to be at risk of severe liver injury if they have ingested paracetamol above the thresholds shown in **TABLE 1**.[2]
   - Regardless of the potential ingested dose, all patients with deliberate-self poisoning should have a serum paracetamol level measured to further refine the risk of hepatic injury and thus the need for acetylcysteine.
   - Adult and paediatric patients without deliberate self-poisoning who are not considered at risk according to the thresholds in Table 1 do not require a serum paracetamol level or LFTs.
4. Following acute overdose, **the most important factor that determines prognosis is the delay beyond 8 hours before the initiation of acetylcysteine**.[2,3]
5. Acetylcysteine is an effective antidote that prevents mortality if administered within 8 hours of an acute overdose. It has also been shown to improve prognosis if administered at any time (beyond 8 hours) following overdose.

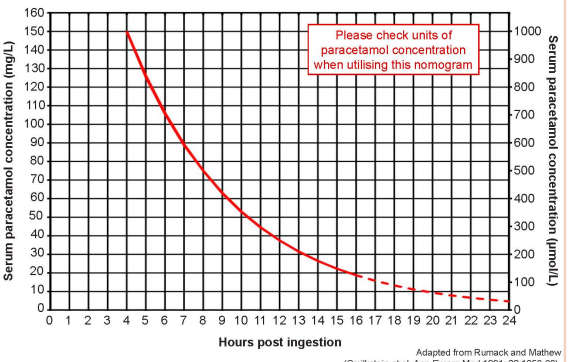
TABLE 1. Paracetamol dosing that may be associated with hepatic injury

	Adults and children over 6 years of age	Children (aged 0-6 years)*
Acute Single Ingestion	> 200 mg/kg or 10 g (whichever is lower) over a period of less than 8 hours.	> 200 mg/kg over a period of < 8 hours.
Repeated Supra-therapeutic Ingestion (RSI)	> 200 mg/kg or 10 g (whichever is lower) over a single 24-hour period. > 150 mg/kg or 6 g (whichever is lower) per 24-hour period for the preceding 48 hours. > 100 mg/kg or 4 g (whichever is lower) per 24-hour period, for more than 48 hours in those who also have symptoms indicating possible liver injury eg. abdominal pain, nausea or vomiting.	> 200 mg/kg over a single 24-hour period. > 150 mg/kg per 24-hour period for the preceding 48 hours. > 100 mg/kg per 24-hour period for more than 48 hours.

* For obese children, the body weight used for calculations should be an ideal body weight.

Paracetamol Treatment Nomogram[9]

- Treat ALL patients with serum paracetamol concentration above the nomogram treatment line.
- Ensure that correct units are used (ie. µmol/L or mg/L).



Adapted from Rumack and Mathew (Smilkstein et al. Ann Emerg Med 1991; 20:1058-63).

Management of Acute Single Ingestions

Decontamination

- Decontamination using 50 g activated charcoal is indicated in cooperative adult patients:
  - Immediate-release paracetamol preparations:
    - Administer within 2 hours if ingestion greater than 10 g or 200 mg/kg (whichever is less).
    - Administer within 4 hours if ingestion greater than 30 g.
  - Modified-release paracetamol preparations:
    - Administer within 4 hours if ingestion greater than 10 g or 200 mg/kg (whichever is less).
    - Administer beyond 4 hours if massive doses ingested.
- Activated charcoal is not indicated in paediatric liquid preparation ingestions.

Liquid Paracetamol Ingestion

Paediatric (< 6 years) liquid paracetamol ingestion

- In children who have possibly ingested more than 200 mg/kg, measure a serum paracetamol level at 2 hours post-ingestion:
  - Acetylcysteine is not required if the 2 hour concentration is < 150 mg/L (1000 µmol/L).
  - If the 2 hour concentration is > 150 mg/L (1000 µmol/L), repeat measurement at 4 hours post-ingestion. Commence acetylcysteine if the 4 hour concentration is ≥ 150 mg/L (1000 µmol/L) as per the paracetamol nomogram.
- For children presenting later than 4 hours post ingestion, treat as per the **Acute Ingestion Management Flow-chart**

Paediatric (≥ 6 years) liquid paracetamol ingestion

- In all cases, other than an isolated accidental liquid paediatric ingestion (< 6 years), treat as per the **Acute Ingestion Management Flow-chart.**

What To Do When The Nomogram Does Not Apply

Staggered Overdose

- A staggered overdose comprises several ingestions over a period of less than 24 hours. The paracetamol concentration should be plotted on the nomogram from the earliest time of ingestion.
- If the patient has taken a staggered overdose of paracetamol at multiple time intervals within the last 8 hours, treat the patient as per the < 8 hours scenario in the **Acute Ingestion Management Flow-chart**.
- If it has been MORE than 8 hours since the first dose, treat the patient as per the > 8 hours scenario in the **Acute Ingestion Management Flow-chart**.

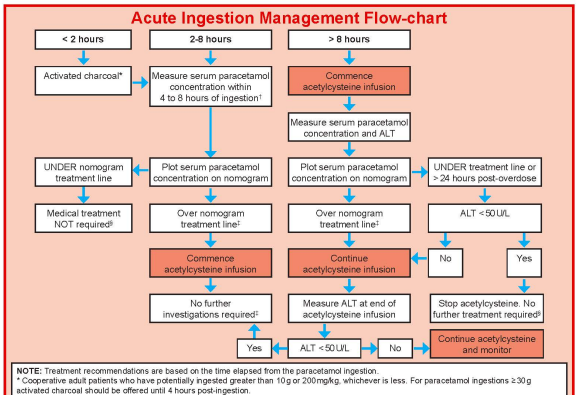
Unknown Time of Paracetamol Ingestion

- If the time of ingestion is unknown, it is safest to treat the patient as a delayed presentation and commence acetylcysteine. If the serum paracetamol concentration is > 10 mg/L (66 µmol/L) or the ALT is elevated > 50 U/L, acetylcysteine treatment should be continued. If further history becomes available and the serum paracetamol concentration can be accurately plotted on the nomogram, this should be done and acetylcysteine discontinued if the paracetamol concentration is below the treatment line.

Sustained-Release Paracetamol Preparations

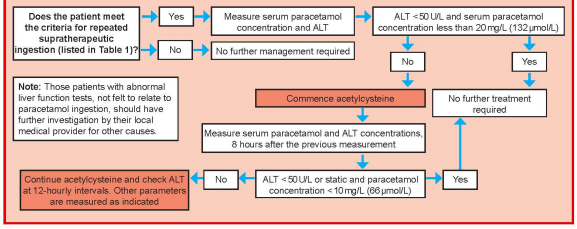
- If more than 10 g or 200 mg/kg (whichever is less) has been ingested commence acetylcysteine.
  - Measure serum paracetamol concentration at 4 or more hours post-ingestion, then again 4 hours later if the first concentration is below the nomogram line.
  - If serial paracetamol concentrations taken 4 hours apart are below the nomogram line and decreasing, acetylcysteine may be discontinued, otherwise continue the full 21 hour course of acetylcysteine to its completion.
- If < 10 g and < 200 mg/kg has been ingested, measure serum paracetamol levels to determine the need for acetylcysteine. Serum paracetamol concentrations should be taken at 4 hours or more post-ingestion (as with standard preparations) and repeated 4 hours later. If either concentration is above the nomogram line, acetylcysteine should be commenced.
- Near the completion of acetylcysteine the patient should have a repeat ALT and paracetamol concentration. Acetylcysteine should be continued if the ALT is increasing (> 50 U/L) or paracetamol concentration is greater than 10 mg/L (66 µmol/L). Acetylcysteine can be continued at a rate of 100 mg/kg of acetylcysteine in 1000 mL of 5% dextrose over 16 hours.

Acute Ingestion Management Flow-chart



NOTE: Treatment recommendations are based on the time elapsed from the paracetamol ingestion.
* Cooperative adult patients who have potentially ingested greater than 10 g or 200 mg/kg, whichever is less. For paracetamol ingestions ≥ 30 g activated charcoal should be offered until 4 hours post-ingestion.
† If paracetamol concentration will not be available until 8 hours post-ingestion, commence acetylcysteine while awaiting paracetamol concentration. ‡Those patients with initial paracetamol concentrations more than double the nomogram line may benefit from an increase in acetylcysteine dose (see text) and serum paracetamol and ALT concentrations should be checked at the end of acetylcysteine infusion.
§ Patients should be advised that if they develop abdominal pain, nausea or vomiting further assessment is required.

Repeated Supratherapeutic Ingestion Management Flow-chart in Adults and Children



Note: Those patients with abnormal liver function tests, not felt to relate to paracetamol ingestion, should have further investigation by their local medical provider for other causes.

Administration of Acetylcysteine

- When required, acetylcysteine is infused in a 3 stage intravenous infusion giving a total dose of 300 mg/kg over 21 hours.[4]
  - **First Infusion:** The initial dose (150 mg/kg) is diluted in 200 mL of 5% glucose and infused over 60 minutes under close medical supervision due to the incidence of anaphylactoid reactions.
  - **Second Infusion:** The second dose (50 mg/kg) is diluted in 500 mL of 5% glucose and infused over the next 4 hours.
  - **Third Infusion:** The third dose (100 mg/kg) is diluted in 1000 mL of 5% glucose is infused over the next 16 hours.
- Acetylcysteine is usually well tolerated. A non-IgE mediated anaphylactic (anaphylactoid) reaction can occur during the initial infusions in 10-50% of patients, manifested by rash, bronchospasm, and rarely, hypotension.[5,6] Management is supportive, with temporary halting or slowing of the infusion and administration of antihistamines and bronchodilators if required.[7] Severe life-threatening reactions are very rare and should be treated with adrenaline as required. Once the symptoms settle acetylcysteine can be recommenced.
- Patients who have serum paracetamol concentrations more than double the nomogram line may benefit from doubling the concentration of the 16 hour infusion of acetylcysteine from 100 mg/kg (current standard acetylcysteine 3rd bag infusion) to 200 mg/kg IV acetylcysteine totalling 400 mg/kg over 21 hours. Serum ALT and paracetamol levels should be checked near the completion of acetylcysteine infusion. Acetylcysteine should be continued if the ALT level is increasing (greater than 50 U/L) or the paracetamol concentration is greater than 10 mg/L (66 µmol/L).
- If hepatic injury is suspected after the third infusion, acetylcysteine is continued at the rate of the last infusion stage (100 mg/kg acetylcysteine over 16 hours or 150 mg/kg/24 hours) until there is clinical and biochemical evidence of improvement.

Acetylcysteine Intravenous Infusion Dosage Guide

- Acetylcysteine is packaged for intravenous infusion in ampoules, each containing a 20% solution (ie. 200 mg acetylcysteine per 1 mL).
- Prescription errors can occur when calculating the dose of acetylcysteine using the recommended mg/kg dose. Using the "Acetylcysteine intravenous infusion dosage guide" allows the dose in mgs and mLs to be calculated and charted in one step, reducing the potential for calculation and transcription errors.[4]
- **TABLE 2** allows calculation of the dose and volume required for each infusion. Patient actual body weight is estimated to the nearest 10 kg.
- The occurrence of a previous reaction does not preclude the use of acetylcysteine on another occasion if indicated.
- It is also important to ensure adequate mixing of acetylcysteine and fluid when preparing the infusion.

TABLE 2. Adult Acetylcysteine Intravenous Infusion Dosage Guide

Patient's body weight (kg)	INITIAL acetylcysteine infusion **Dose:** 150 mg/kg over 60 min to be added to 200 mL of 5% glucose	SECOND acetylcysteine infusion **Dose:** 50 mg/kg over 4 hours to be added to 500 mL of 5% glucose	THIRD acetylcysteine infusion **Dose:** 100 mg/kg over 16 hours to be added to 1000 mL of 5% glucose
	Dose acetylcysteine (g) = volume (mL)* = *(0.75 x wt (kg))*	Dose acetylcysteine (g) = volume (mL)* = *(0.25 x wt (kg))*	Dose acetylcysteine (g) = volume (mL)* = *(0.5 x wt (kg))*
50	7.5 g = 37.5 mL	2.5 g = 12.5 mL	5 g = 25 mL
60	9 g = 45 mL	3 g = 15 mL	6 g = 30 mL
70	10.5 g = 52.5 mL	3.5 g = 17.5 mL	7 g = 35 mL
80	12 g = 60 mL	4 g = 20 mL	8 g = 40 mL
90	13.5 g = 67.5 mL	4.5 g = 22.5 mL	9 g = 45 mL
100	15 g = 75 mL	5 g = 25 mL	10 g = 50 mL
110†	16.5 g = 82.5 mL	5.5 g = 27.5 mL	11 g = 55 mL

* Assuming concentration of acetylcysteine is 200 mg/mL.
† **Note:** All patients weighing greater than 110 kg should be dosed according to a bodyweight of 110 kg.

- In children the volume of 5% glucose into which acetylcysteine is diluted should be an appropriate volume for the patient's weight. Eg.:
  - **Children ≤ 20 kg body weight:**

    150 mg/kg acetylcysteine in 3 mL/kg 5% glucose over 60 minutes
    followed by 50 mg/kg in 7 mL/kg 5% glucose over 4 hours
    followed by 50 mg/kg in 7 mL/kg 5% glucose over 8 hours
    followed by 50 mg/kg in 7 mL/kg 5% glucose over 8 hours.
  - **Children > 20 kg body weight:**

    150 mg/kg acetylcysteine in 100 mL 5% glucose over 60 minutes
    followed by 50 mg/kg in 250 mL 5% glucose over 4 hours
    followed by 50 mg/kg in 250 mL 5% glucose over 8 hours
    followed by 50 mg/kg in 250 mL 5% glucose over 8 hours.

Recommendations of when to call the Poisons Information Centre:[8]

Very large overdoses: • Immediate release or modified release paracetamol overdoses of > 50 g or 1 g/kg (whichever is lower). • A very high paracetamol concentration, > double the nomogram line.
Intravenous paracetamol errors/overdoses.
Patients with hepatotoxicity (e.g. ALT > 1000 IU/L).

* These are situations where the risk of hepatotoxicity may be greater, the optimum advice is potentially changing and where it may be most useful to seek advice.

- This guideline addresses the majority of paracetamol ingestion scenarios encountered. However not all clinical scenarios can be addressed, or the management remains controversial.
- Where there are any concerns regarding the management of paracetamol ingestion, advice should always be sought from a clinical toxicologist or local Poisons Information Centre.

References
1. Sheen CL et al. (2002) QJM 95(9):609-619. **2.** Dart RC et al. (2006) Clin Toxicol (Phila) 44(1):1-18. **3.** Smilkstein MJ et al. (1988) N Engl J Med 319(24):1557-1562. **4.** Little M et al. (2005) Med J Aust 183(10):535-536. **5.** Sandilands EA & Bateman DN. (2009) Clin Toxicol (Phila) 47(2):81-88. **6.** Lynch RM & Robertson R. (2004) Accid Emerg Nurs 12(1):10-15. **7.** Bailey B & McGuigan MA. (1998) Ann Emerg Med 31(6):710-715. **8.** Ferner RE et al. (2001) Br J Clin Pharmacol 52(5):573-577. **9.** Chiew AL et al. (2015) Med J Aust 203(5):215-218.

These guidelines are not meant to be prescriptive. Each case should be considered individually. Health care professionals should use their clinical judgement to determine the most appropriate course of action. If in any doubt the Poisons Information Centre should be contacted. Prepared in consultation with Angela L Chiew,[1,2] John S Fountain,[3] Andis Graudins,[4,5] Geoffrey K Isbister,[6] David Reith[7,8] and Nicholas A Buckley.[9]

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Revised and updated in September 2016
(version 5)
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10.2 Appendix 2:
Paracetamol Overdose Guidelines: Sweden

Giftinfo – för läkare
Swedish Poisons Information Centre

acetaminophen

⚠

Risk of serious, hard-to-treat poisoning!

Call for slightest uncertainty or need for further information Gift Information Center 010-456 67 19

Summary

Paracetamol itself has a low acute toxicity, but in overdose a toxic metabolite is produced which can induce liver necrosis. Initial symptoms are missing. The liver affects debut after 1-1.5 days with increasing transaminases. Maximal liver effect is usually seen after 3-4 days. Risk of fulminant hepatic failure with coagulation disorders, encephalopathy and circulatory failure. Antidote exists. Acetylcysteine inserted within 8-10 hours provides virtually complete protection against liver damage. However, in the case of overdose of depot preparation (Alvedon 665 mg), the maintenance dose of acetylcysteine must be doubled.

Symptoms / findings

Nausea and vomiting may occasionally occur within the next few hours following an overdose. These symptoms usually resolve within 1 day. Lack of abdominal pain may occur later on.

Stubborn PK increase is often seen after about ½ days. This early increase is not due to liver damage but to the fact that paracetamol inhibits vitamin K-dependent coagulation factors.

Signs of liver effect with increasing transaminases, and elevated PK, are seen after 1-1.5 days. In case of severe poisoning, liver failure develops with coagulation disorders, hypoglycaemia and consciousness reduction.

Renal impairment can sometimes be seen in combination with liver failure, but also exceptionally in patients without liver.

Metabolic acidosis is unusual but occurs in severe poisoning both early in the process and late in severe liver injury.

Consciousness may occur at an early stage at very high serum concentrations of paracetamol (approximately 5000 micromol / l).

Sampling / investigations

Blood samples for determination of serum concentration of paracetamol are taken when 4 hours elapsed since intake. Should the patient be hospitalized later, samples will be taken as soon as possible. The sample taken before acetylcysteine may be inserted because some analytical systems may otherwise show false to low values of s-paracetamol.

NON-BREAKING HYPHEN (8209) DEPOT PREPARATION: Repeated sampling is only required when concomitant use of drugs that inhibit the motility of the gastrointestinal tract (primarily opiate). Then a new sample is taken 2 hours after the first and if the serum concentration is increasing then new samples are taken at 2 hour intervals. In these cases, maximum serum concentration may be delayed for many hours. In case of toxic serum concentration (see below Monitoring / Treatment) acetylcysteine is inserted. Thereafter, no further sampling for s-paracetamol is needed unless the serum concentration is very high (guideline approximately 3000 micromol / l). In these cases, a new sample is taken before acetylcysteine infusion is terminated and if paracetamol remains in the blood, the treatment is prolonged.

DEPOT PREPARATION (Alvedon 665 mg): In case of overdose of depot preparations, s-paracetamol is taken at the time of 4, 6, 12 and 18 hours although acetylcysteine treatment is in progress (a high concentration late in the course of treatment may occasionally justify further dose increase of the antidote). Incoming the patient later than after 4 hours, sample immediately and then according to the schedule. If the serum concentration rises but is below the toxic concentration, the samples are taken tighter, at 2 hour intervals. In these cases, maximum serum concentration may be delayed for many hours. Acetylcysteine is inserted if any of the samples exceed the treatment limit for risk patients (eg 650 micromol / l at 4 hours). Note See below special dosage for this type of preparation.

TOTAL PREPARATION: AST, ALT, PK, blood status, s-creatinine, electrolyte status and blood sugar are taken on arrival. AST, ALAT and PK are then taken once a day in all patients in which acetylcysteine treatment is indicated. In case of established liver affect, these samples are taken 2- (3) times per day. If liver and s-creatinine are normal 36 hours after overdose no additional controls are required.

In case of affected general conditions, acid-base status and lactate are taken.

Monitoring / Treatment

Ventricular rinse is rarely indicated. If taken> 140 mg / kg <2 hours before arrival, carbon is given. A further dose of carbon is given after 2-4 hours in case of overdose of depot preparation (Alvedon 665 mg).

If the intake dose is suspected to be toxic (adults> 140 mg / kg, children> 175 mg / kg) and s-paracetamol can not be obtained within 8 hours after the overdose, acetylcysteine is inserted without waiting for test responses.

NON-DEPOT PREPARATION: Acetylcysteine is inserted if s-paracetamol is above 1000 micromol / l at 4 hours, 700 micromoles / l at 6 hours, In case of starvation, dehydration, hepatic impairment or treatment with the enzyme inducing drugs phenobarbital or isoniazid, lower limits apply: 650, 450, 325 and 230 micromol / l respectively.

DEPOT PREPARATION (Alvedon 665 mg): Acetylcysteine is inserted if s-paracetamol is above 650 micromol / l at 4 hours, 450 at 6 hours, 325 at 8 hours or 160 micromol / l at 12 or 18 hours after overdose.

ADDITIONAL PREPARATION
If the patient arrives 24-36 hours after ingestion of suspected toxic dose and has symptoms or if paracetamol is detectable in serum, acetylcysteine is inserted.

If the patient arrives> 36 hours after the overdose and has normal liver tests, treatment-intensive inx may be excluded.

In case of repeated "therapeutic" overdose, acetylcysteine may be indicated. RING GIC.

If liver effects are observed, acetylcysteine treatment may be indicated regardless of the time frame. RING GIC

ACETYLCYSTEIN ON OVERDELATION OF NON-BREAKING HYPHEN (8209) DEPOT PREPARATION: Intravenously, initially 150 mg / kg in 200-300 ml glucose 50 mg / ml or isotonic NaCl for 15 minutes, then 50 mg / kg in 500 ml glucose 50 mg / ml for 4 hours , 5 mg / kg / hour) and then 6.25 mg / kg / h for 16 hours or longer, see below (practically 75 mg / kg is dissolved in 500 ml and given during each 12-hour period).

ACETYLCYSTEIN FOR OVERDOSING DEPOT PREPARATION:

In these cases (Alvedon 665 mg), the usual bolus dose of 150 mg / kg is given in 200-300 ml of isotonic glucose or saline solution in 15 minutes. Subsequently, maintenance treatment with acetylcysteine is given 12.5 mg / kg / h for at least 20 hours (practically 150 mg / kg is dissolved in 500 ml and given during each 12-hour period). Before discontinuing acetyl treatment, check that s-paracetamol is not detectable.

TOTAL PREPARATION: The amount of liquids can be reduced if necessary, especially the dilution schedule is available. See Special Actions.

Prolonged treatment with acetylcysteine may be relevant for late treatment, repeated "therapeutic" overdose, detectable paracetamol concentration after 20 hours of antidote treatment or liver effect. RING GIC.

In case of side effects (nausea, urticaria, itching most commonly) temporarily close the infusion and give antihistamine (for example orodispersible desloratadine 10 mg or intravenous Tavegyl 2 mg). RING GIC.

Acetylcysteine can be administered orally, but causes frequent vomiting, which is why intravenous administration is recommended primarily. RING GIC.

MARS dialysis and liver transplantation may be relevant. RING GIC.

Toxicity / concentrations

One-time administration of adults, toxic dose: 140 mg / kg

Disposable child, toxic dose: 175 mg / kg

Repeated intake for several days of higher doses than recommended in adults in conjunction with solid, fluid or alcoholism caused severe hepatic impairment. RING GIC.

Repeated for large doses to children. RING GIC.

For toxic serum concentrations see Monitoring / Treatment.

Occurrence / Preparation

Also present in many combination preparations. Available as a depot preparation.

Content

keyword

Acetaminophen, NAPA, N-acetyl-p-aminophenol, propacetamol, Alvedon, Alvedon forte, Curadon, Curadon forte, Panodil, Panodil Bread, Panodil Extend, Panodil Forte, Panodil Zapp, Pro-Dafalgan, Perfalgan, Reliv, Citodon, Panocod

Release Info

Factualized **January 10, 2017** by the Poison Information Center

i

About the Poison Information Center's database for doctors

The articles in this database have been designed to be used exclusively by doctors and should be seen as a complement rather than an alternative to GIC's telephone consulting.

Negations are not usually used in the texts (for example, if dialysis is not mentioned, there is also no treatment option).

For combination preparation, see if necessary FASS, as the search function is not comprehensive for these.

Immediately contact GIC with the least doubt regarding the meaning of the articles.

Due to the fact that the information is a fresh item, prints of the articles may not be multiplied and distributed, nor should the articles be stored in the disconnected mode.

To be easy-to-use and useful, the database needs to concentrate on the most practical, why more odd details about symptomatology and treatment may be missing. Therefore, it is important to take into account the text of the frequently repeated call to contact GIC.

10.3 [Appendix 3: Modeling and simulation analysis of paracetamol concentrations in the overdose setting

Population pharmacokinetic model

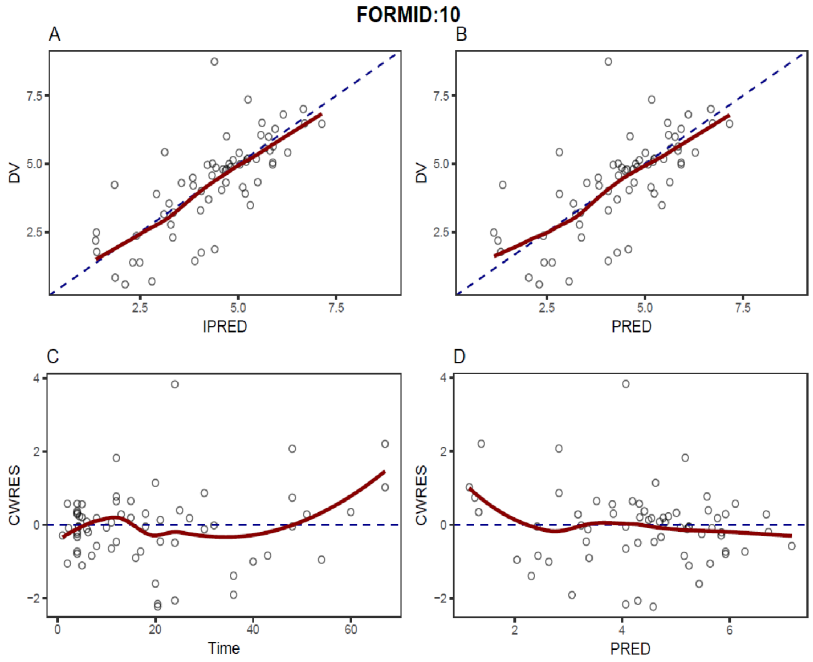
A population pharmacokinetic model has been developed to describe the changes in paracetamol serum concentrations over time for GSKCH marketed IR and MR paracetamol single ingredient formulations in the therapeutic and overdose settings. For this effort, a mixed effects model comprised of a structural model, describing the time course of drug concentration, and a statistical model, quantifying the variability within the population was created. In the mixed effects modeling approach, structural and stochastic parameters are simultaneously estimated by fitting the model to the data. Estimates of variance on all individual parameters and residual effects were assessed allowing for individual predictions of paracetamol plasma concentrations.

Data from 28 subjects receiving IR paracetamol under therapeutic conditions, 27 subjects receiving MR paracetamol under therapeutic conditions, 52 patients who were exposed to IR paracetamol in the overdose setting, and 219 patients who were exposed to MR paracetamol in the overdose setting were used to build the model. The therapeutic data was obtained from an internal GSKCH relative bioavailability study with intensive sampling, the IR overdose data was obtained from the GSKCH post marketing safety database, and the MR overdose data was obtained through request of poison information centers in Australia and case data from Sweden provided by PRAC.

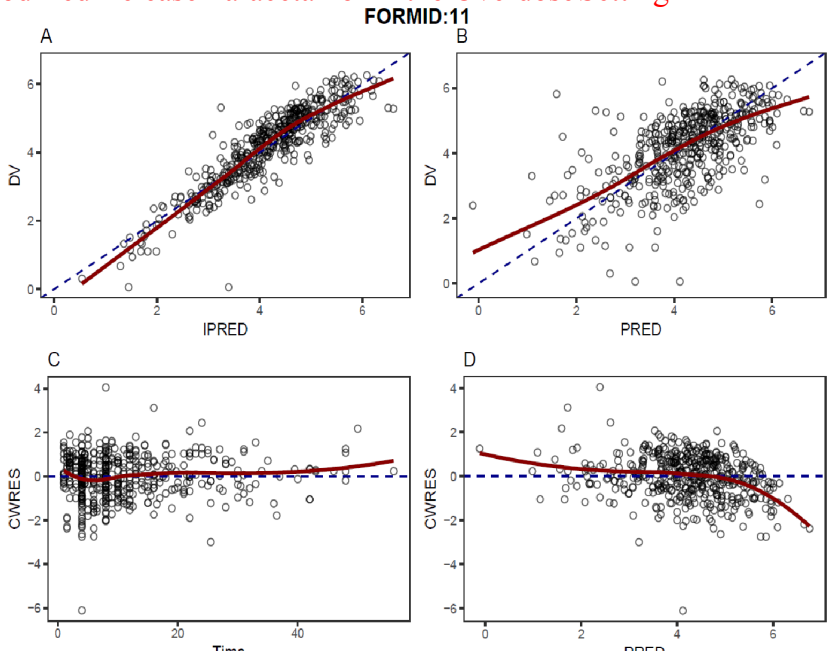
The resulting model is a two compartment model with combined first and zero order absorption and a lag time before absorption. Linear clearance is observed at therapeutic levels and is altered in the overdose setting. As shown in Figure A the model was able to describe both the IR and MR paracetamol pharmacokinetic levels in the overdose setting well. There is a small amount of deviation from the line of unity at the extrema of the observed concentrations, but this is likely a function of the limited observations at the very lower and higher ends of the concentrations. Overall, the model is a good fit of the observed data.

Figure A: Goodness of Fit Plots for (a) Immediate and (b) Modified Release Paracetamol Formulations

- Immediate Release Paracetamol in the Overdose Setting



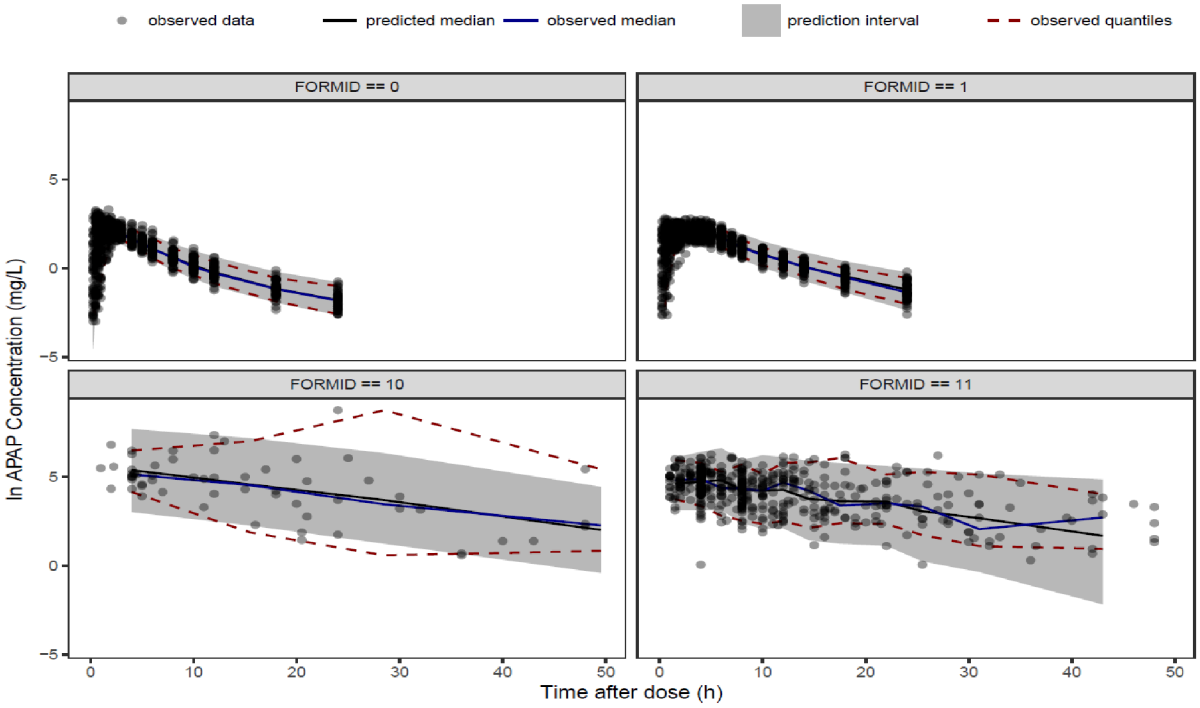
- Modified Release Paracetamol in the Overdose Setting



Note: DV = Dependent Variable, Paracetamol Observed Concentrations (ln mg/L), IPRED = Individual Predicted Concentrations (ln mg/L), PRED = Population Predicted Concentrations (ln mg/L), Time = Time (h), CWRES = Conditional Weighted Residual

A Visual Predictive Check of the predictability capacity of the model is presented in Figure B. For all four conditions, it can be seen that the model predicts very well the observed data over the entire range of concentrations. This is evident by the fact that almost all of the observed concentrations are contained within the prediction intervals of the model. The predictive ability of the developed mode allows for a confident characterization and simulation of paracetamol concentrations in the overdose setting for both IR and MR formulations. Further detail on the model building process, final parameters, and diagnostic evaluation of the robustness of the model can be provided upon request.

Figure B: Visual Predictive Check



Note: Clockwise from Top Left: IR Therapeutic Setting; MR Therapeutic Setting; MR Overdose Setting; IR Overdose Setting

Simulation analysis

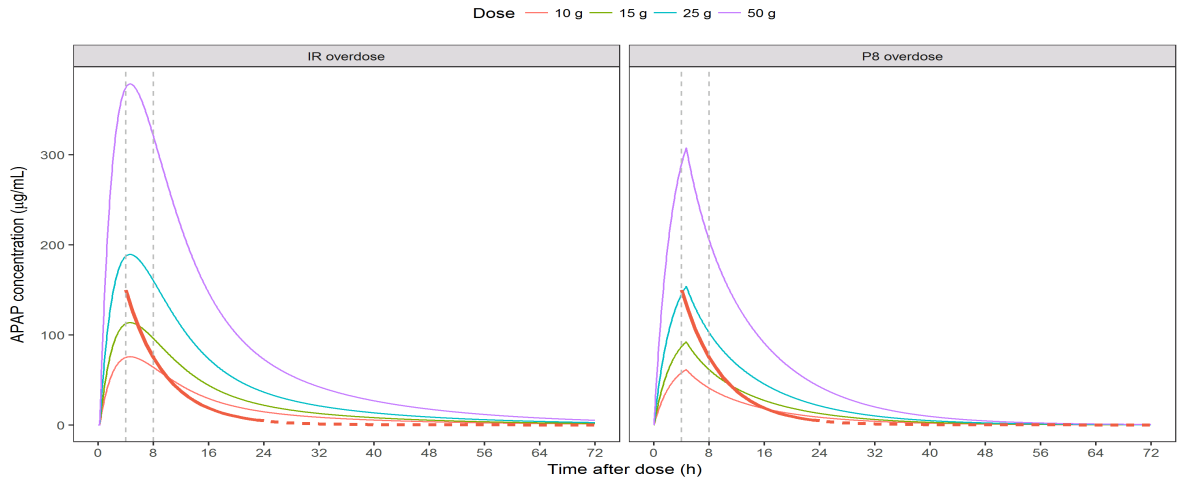
As hypothesized, overdoses with the immediate release formulation can only be described when a shorter duration for absorption is allowed compared to the modified release formulation. The final population means for time of absorption are approximately 2 and 4 hours for the IR and MR formulations respectively. This results in higher plasma concentrations of paracetamol for the IR relative to the equivalent dose of MR at early time points after ingestion as seen in Figure C. This allows for timely intervention (within 8 hours of ingestion) with acetylcysteine in cases of overdose with the IR formulation.

The elimination phase for paracetamol is prolonged for both the IR and MR formulations in the overdose setting relative to therapeutic doses as demonstrated in

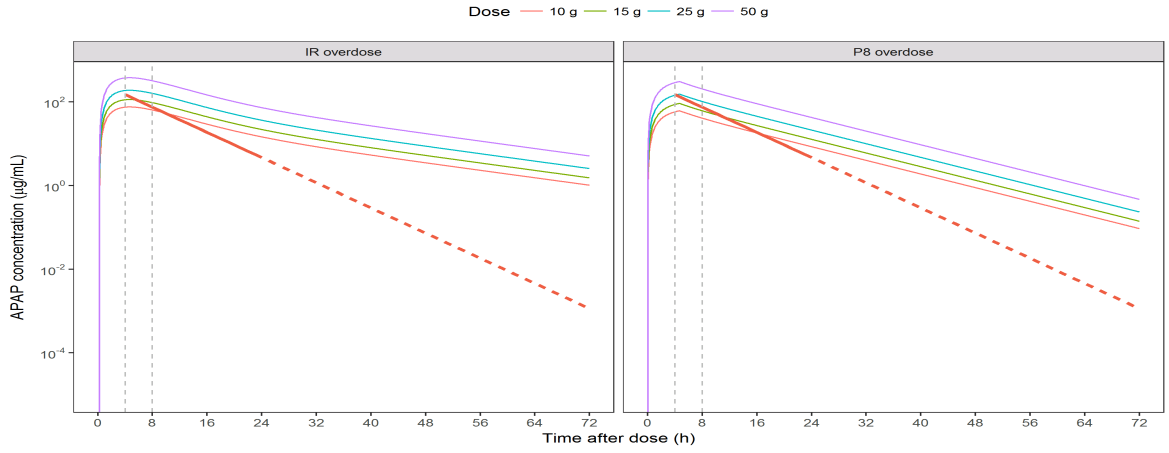
both the observed and simulated data (plots of observed data can be provided upon request). This is consistent with previous publications (Slattery and Levy 1979) stating the same and the hypothesis that once paracetamol is absorbed the clearance mechanisms are formulation independent. Interestingly, the slope of the elimination phase appears to be similar at the various overdose levels suggesting a leveling off after saturation of initial clearance mechanisms. The simulated data also suggests that for equivalent doses of IR and MR, especially at very high doses, prolonged elevated concentrations are possible for both formulations, with concentrations possibly remaining higher for the IR formulation due to the higher initial peaks. This is corroborated by observed case studies and the data presented herein (Smith et al 2008).

Figure C: Simulations of Paracetamol Serum Concentrations over Time for Immediate and Modified Release Doses of 10, 15, 25, and 50 g

(a) Linear Scale



(b) Log Scale



Note: IR = Immediate Release Formulation; P8 = Modified Release Formulation

Additional observations from simulations of overdoses of 10 g (20 tabs IR, 15 tabs MR), 15 g (30 tabs IR, 22 tabs MR), 25 g (50 tabs IR, 37 tabs MR), and 50 g (100 tabs IR, 75

tabs MR) of MR paracetamol indicate that doses above 10 g appear to have the potential to be above the nomogram line within 24 hours (approximately 17 hours). For 10 g and 15 g overdoses it does not appear that this level is significantly above the nomogram line (toxicity has been associated with concentrations 3-fold greater than the nomogram line [Marks et al 2017]); however, from analysis of the pharmacovigilance data hepatotoxicity is possible within this range of overdose.

The observation from the simulations that doses above 10 g are the first dose level to meaningfully cross the treatment nomogram line is consistent with the recommendations of the Australian nomogram suggesting that doses of MR paracetamol above 10 g receive antidote treatment immediately irrespective of paracetamol concentrations.

For doses of 25 g, for the MR formulation, the nomogram is crossed at 4.15 hours. The elevated concentrations appear to persist for approximately 40 hours as per the simulations and 24 hours per observations. For 50g doses and above of MR paracetamol, the elevated concentrations persist for at least 48 hours. This is true for IR formulations as well. At these dose levels, it can be expected that paracetamol concentrations will remain elevated for at least 48 hours.

Another finding from the modeling exercise is that at 4 and 8 hours, only about 68 and 88% of the MR paracetamol dose is projected to be absorbed. Approximately 92% of an IR dose is expected to be absorbed at 8 hours post ingestion. As solubility capacity is exceeded and the potential for bezoar formation is increased with higher doses of the MR formulation, the percentage absorbed at a given point in time may be expected to decrease. As may be expected, with large overdoses of the MR formulation, with meaningful proportions of drug left to absorbed, prolonged elevated concentrations are not surprising. Consistent with clinical practice, it is therefore recommended that monitoring for signs and symptoms of hepatotoxicity, LFT levels, and paracetamol serum concentrations be considered for this period of time with corresponding acetylcysteine treatment when appropriate according to LFT levels and clinical presentation.

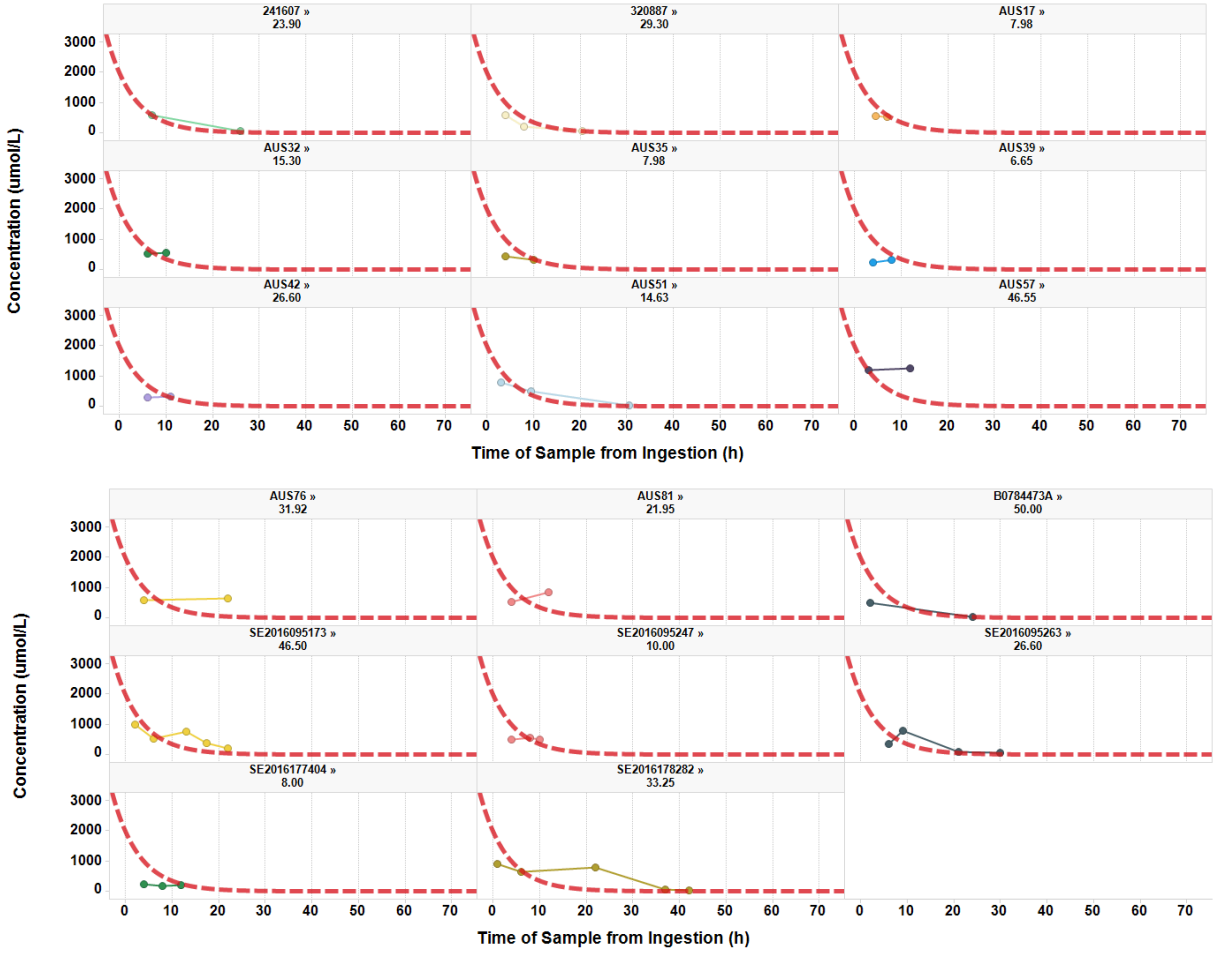
Late line crossers

One of the main concerns with the MR paracetamol formulations is the issue of late nomogram line crossers, whereby the initial presence of concentrations below the nomogram line within the designated 4 – 8 hour window appears to reject the need for antidote treatment only to cross the nomogram line at a later point in time, resulting in late initiation of antidote intervention. This is of importance since data available in published literature regarding paracetamol overdose indicates that initiation of n-acetylcysteine within 8 hours of overdose is critical to positive outcomes relative to cases initiating antidote after 8 hours (Vale and Proudfoot 1995). This highlights the need to consider initiation of antidote when time of ingestion or dose are not known for either IR or MR formulations.

In this analysis, late line crossers were defined as those cases that had concentrations within the 4 – 8 hours time window that would have indicated no need for acetylcysteine treatment and then had a later serum paracetamol measurement that

would have indicated the need for treatment. In the obtained cases, there were 17 instances (1 case with IR formulation [BO784473A]) of late line crossers as defined above. As can be observed (Figure D), the majority of the cases with the late line crossing had ascending or flat concentration time profiles from the time of first observation to the time of nomogram crossing. The remaining cases had descending curves; however, the elimination half-life of that corresponding curve, as determined by calculating the slope of the line on a natural log scale, exceeded 4 hours.

Figure D: Concentration vs Time Profiles of Late Line Crossers



Note: First value in title of each chart is subject number followed by dose in grams

With respect to identifying overdose cases with below threshold concentrations within the 4 – 8 hour post ingestion timeframe which then cross the threshold post 8 hours, the observed cases and modeling suggest that a sampling of 3 time points within 4 – 8 hours, with the middle time-point ideally being 6 hours post ingestion, provides a good indication as to whether concentrations will remain elevated and cross the nomogram treatment line. If the slope of the line is flat or ascending, it will likely result in prolonged elevated concentrations. Moreover, if all three points are descending and the calculated half-life is 4 hours or greater, it is likely that subsequent concentrations will be above the nomogram, especially if the concentrations between 4 – 8 hours are close

to the nomogram line. Calculating the elimination half-life based on the three points will allow for a projection of subsequent concentrations in half-life intervals based on the last measured concentration. This may indicate a need to initiate treatment if these values are below the nomogram, especially if projected subsequent levels are 2 times greater than the corresponding nomogram value (Marks et al 2017). Importantly, half-lives > 5.5 hours have been associated with liver toxicity (Schiodt et al 2002), so having 3 points would ideally allow for the calculation of this value and initiate treatment. It is essential that the 3 time points (within 4 – 8 hours) and assessment of half-life be obtained in a time-frame that allows for initiation of acetylcysteine within 8 hours if it is required. If the assessment will not be available until > 8 hours post ingestion, commence acetylcysteine while awaiting the concentration values and calculation.

Pharmacokinetic-pharmacodynamic model for optimal acetylcysteine dosing

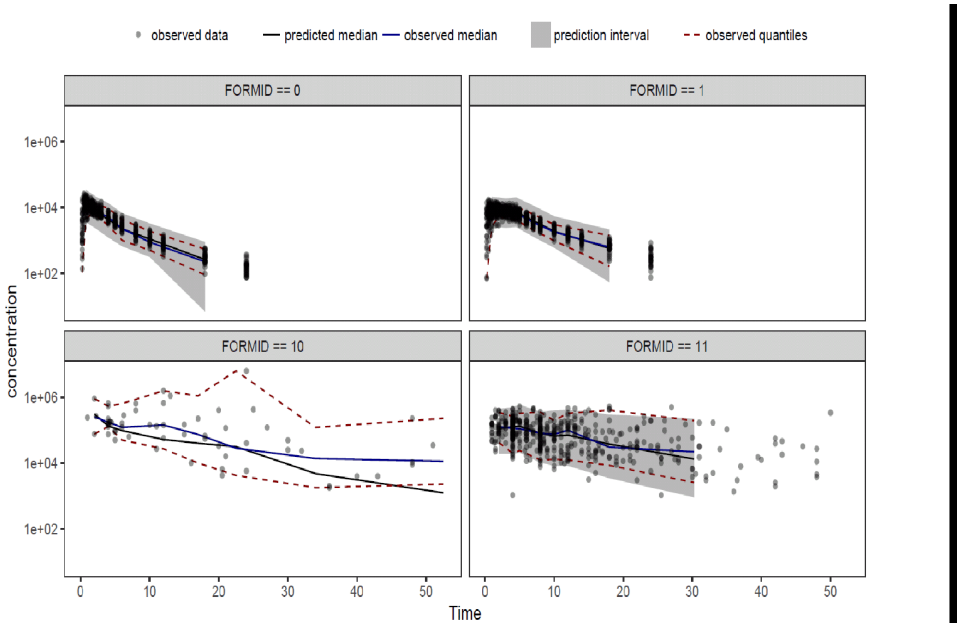
Separately, efforts were made by GSKCH to develop a pharmacokinetic-pharmacodynamic model in order to inform optimal dosing of acetylcysteine. It is observed in the literature as well as in the analysis of pharmacovigilance data presented herein, that in the very high overdose setting (ingestion of 30 g or greater), treatment with the standard acetylcysteine regimen is not effective in a limited amount of cases with either of the IR or MR formulations. This is a reflection of the fact that when the acetylcysteine regimen was originally established, the dosing was determined empirically on a weight basis and not on a stoichiometric basis of neutralization of NAPQI associated with a corresponding paracetamol dose (Bateman and Dear 2017). It is recognized that in order to perform such a stoichiometric analysis, data on direct measurement of paracetamol toxic pathway metabolites, specific and sensitive livery injury markers, paracetamol PK data, glutathione levels, and n-acetylcysteine concentrations may be necessary (Marks et al 2017, Bateman and Dear 2017). Unfortunately, as per the requirements of the nomogram, typically only paracetamol concentration data and LFT measurements are collected. Moreover, this data is not uniformly collected and typically when soliciting poison information centers, only PK data was found to be collected consistently. To add to the challenge, many poison information centers are not willing to share patient level data even in a de-identified fashion. Efforts were made to obtain data from the Australian Paracetamol Project, which is in possession of a database containing some of the critical information detailed above on a patient level; however, to this date, the data has not been shared with GSKCH. To this effect, the available data did not allow for a quantitative analysis of whether the acetylcysteine dose / concentrations were sufficient for the corresponding paracetamol dose.

In order to optimize the utility of the available data, a physiologically based pharmacokinetic (PBPK) model was created based on the methods by Zurlinden et al 2016. The intended outcome of this model was to predict intrahepatic concentrations of paracetamol from serum levels and subsequently predict the corresponding levels of NAPQI and toxic protein conjugates. This could then corroborate the findings of the POP PK model in terms of the duration of risk of hepatotoxicity after a given dose of paracetamol. The visual predictive check for the model is presented in Figure E. As can be seen from the figures below, the PBPK model is predictive of the overdose dosing

scenario for the MR formulation with the exception of time points beyond 30 hours. This is due to the fact that the Zurlinden model was designed up to the time interval of 12 hours; however, with modifications to the rate constants for glucuronidation and sulfation processes based on the observed pharmacokinetic profiles from the overdose cases, the time interval for the model was extended. As more data becomes available and the model is further optimized, the interval covered by the model can be further extended. As such, currently, these predictions cannot be relied upon to inform the profiles of intrahepatic paracetamol, NAPQI, or protein conjugate levels for the entire time interval for which paracetamol concentrations are expected to remain elevated after an overdose. This again relates to the robustness of the available data derived from uncontrolled poison information center reports.

The challenge of optimizing the dose and duration of acetylcysteine treatment for corresponding paracetamol dose is recognized by experienced investigators in the field (Bateman and Dear 2017). It is further recognized that efforts to refine this treatment paradigm are ongoing and that currently the requisite data for optimizing the regimen are not consistently collected. Overall, the modeling and simulation efforts are promising, and further evaluation of the PBPK in conjunction with population PK approaches will allow for precise characterization of different sources of variability. These are areas of investigation that GSKCH will continue to pursue in particular as more robust data becomes available. In the interim, treatment of high paracetamol overdose should continue per current practice of close monitoring of signs and symptoms of liver injury with direct measurement of paracetamol concentrations and ALT levels.

Figure E: Visual Predictive Check of PBPK Modeling



Note: Clockwise from Top Left: IR Therapeutic Setting; MR Therapeutic Setting; MR Overdose Setting; IR Overdose Setting ; Concentration = APAP $\log_{10}$ µg/L

Upper threshold for treatment

The data modelling exercise using simulations of overdoses of 10, 15, 25, and 50 g of MR paracetamol indicates that at all such doses, serum paracetamol may cross the Rumack-Matthew treatment nomogram line at some point within 24 hours of ingestion. In such patients, initial measurements of serum paracetamol (e.g. levels taken at 4 hours or more post-ingestion and repeated 4 hours later) may indicate that treatment with acetylcysteine is not necessary. However, patients who are 'late line crossers' (in whom serum paracetamol rises at later time points) may be at risk of hepatotoxicity if not appropriately treated. For this reason, GSKCH proposes that treatment with acetylcysteine should be considered in anyone who is suspected to have taken an overdose of MR paracetamol or unknown paracetamol tablet of 10 g or more, rather than relying solely on measurements of serum paracetamol to determine whether or not to treat with acetylcysteine.

This dose-based approach is consistent with the published Guidelines for the management of paracetamol poisoning in Australia and New Zealand (Chiew et al 2015). Since 2001, these guidelines have offered advice for the management of overdose of MR paracetamol, and in 2008 were updated to include the specific advice that acetylcysteine treatment should be started immediately if more than 200 mg/kg or 10 g (whichever is less) has been ingested (Daly et al 2008). Tan and Graudins (2006) recognised the potential for slow absorption of modified release paracetamol and thus a delayed peak serum paracetamol concentration above the nomogram line, and concluded that the paracetamol treatment nomogram might not reliably predict hepatotoxicity. The more recent 2015 update of the guidelines offers further guidance in which serial paracetamol and alanine aminotransferase (ALT) concentrations are used to determine the duration of acetylcysteine treatment in MR paracetamol overdose. However, the advice to initiate acetylcysteine treatment following ingestion of 200 mg/kg or 10 g (or more) of MR paracetamol remains.

In a review of acetylcysteine for the treatment of paracetamol toxicity in paediatric patients, Algren (2008) suggests that ≥150 mg/kg may be a conservative threshold for potentially toxic acute ingestion of paracetamol, and up to 200 mg/kg had been ingested without development of toxicity (especially in children). Nevertheless, a threshold for initiation of acetylcysteine treatment of 10g (or more) of MR paracetamol is likely to ensure that patients with atypical serum paracetamol measurements (i.e. those who have late 'rebound' elevations in serum paracetamol) receive appropriate acetylcysteine treatment.

Multiple sampling

The results of the modeling exercise demonstrate that multiple serum samples (n=3) between 4-8 h after ingestion provides the ability to calculate the slope of the serum paracetamol line, and half-life of paracetamol.

To identify potential late line crossers sampling of 3 time points within 4 – 8 hours of ingestion provides a good indication as to whether concentrations will remain elevated. If the slope of line is flat or ascending it will likely result in prolonged elevated concentrations. Moreover, if serum paracetamol levels at all three sample points are

descending and the calculated half-life is >4 hours, it is likely that this will result in concentrations above the Rumack-Matthew treatment nomogram later. In addition multiple serum paracetamol levels will provide an estimate of how long serum paracetamol will remain elevated. There are however isolated instances where a sharp decline in concentrations occurred with a subsequent rebound post 8 hours. These are not the typical profile and do not seem to be related to dose. This reinforces the need to initiate treatment on subjects with reported overdose of 10 g or greater to capture these non-typical profiles of overdose.

In humans, the half-life of paracetamol in blood after a therapeutic dose is 1.5 – 3 h, but increases after toxic doses and with liver injury (McGill and Jaeschke 2013). Half-lives > 5.5 hours have been associated with liver toxicity (Schiodt et al. 2002). The use of half-lives however does not represent current clinical practice in the management of paracetamol overdose and would represent a significant change to existing practices.

As an alternative, it is recommended that further samples should be considered if serum paracetamol concentrations are not declining. This approach is consistent with the published Guidelines for the management of paracetamol poisoning in Australia and New Zealand (Chiew et al 2015).

Time period for monitoring

The results of the modeling exercise demonstrate that serum paracetamol levels with MR paracetamol can be elevated from up to 24 h with 10 g, up to 40 hours with 25 g and 48 h with 50 g.

For early presentations (<10 h) and those who present within 24 h the modeling and simulation exercise provides the guidance for the treating physician, that patients may need to be monitored for an extended period of time beyond what would be applicable for IR paracetamol based on dose, however with appropriate clinical care, and serum sampling, patients who have ingested MR paracetamol can be adequately monitored and treated with favorable outcomes.

Data available in published literature regarding paracetamol overdose indicates that initiation of acetylcysteine within 8 hours of overdose is critical to positive outcomes with cases initiating antidote after 8 hours resulting in significantly increased relative risk of morbidity and mortality (Vale and Proudfoot 1995, Brok, et al 2006).

The pooled data from clinical trials associated with acetylcysteine treatment have assessed the use of acetylcysteine based on presentations up to 24 hours (Brok, et al 2006). For patients who present >24 h it is recommended that the patient is assessed to determine if they are at risk of hepatic injury. In certain situations where established hepatotoxicity is present Wallace et al, recommend contacting the National Poisons Information Service, or a hepatologist at a liver transplant unit for tailored advice in the management of the patient, as meticulous supportive care is critical to a good outcome in such cases (Wallace, et al 2002).

Due to elevated serum paracetamol concentrations extending for up to 48 h at 50 g and based on available evidence from literature and review of the worldwide GSK safety

database, that the benefits of prolonged acetylcysteine treatment outweigh any incremental risk and is recommended for use in treating patients following overdose with MR paracetamol.

Acetylcysteine acts as a precursor for the synthesis of glutathione, and therefore maintains cellular glutathione at a level sufficient to inactivate NAPQI, the toxic metabolite of paracetamol. There is a stoichiometric relationship between acetylcysteine and NAPQI that determines the neutralization efficacy of acetylcysteine that is dependent on the concentration of both acetylcysteine and NAPQI. For such reasons, higher doses of paracetamol overdose, irrespective of formulation, may require increased acetylcysteine doses or prolonged acetylcysteine infusion duration. Marks et al, 2017 note that data on direct measurement of current and novel hepatic biomarkers such as NAPQI, specific and sensitive liver injury markers, glutathione, and n-acetylcysteine concentrations would inform such an evaluation. Chiew et al 2017 concur that the data to establish these relationships requires further research. Although massive overdoses (>30g) can currently be successfully managed by careful monitoring of clinical presentation and laboratory measures, there is opportunity to refine and optimize the utilization of acetylcysteine in these cases.

Summary and recommendations

The following summary of observations from the modeling and simulation exercises performed by GSKCH and previous experience in the management paracetamol overdose:

- Modeling confirms that IR formulation has faster absorption than MR leading to higher peaks at the same time point allowing for easier identification for timely treatment compared to MR
- Modeling also confirms that IR and MR formulations experience similar prolonged elimination in the overdose setting resulting in prolonged exposures. It may also be possible that the IR formulation experiences higher paracetamol concentrations over the same duration due to the initial faster absorption
- Late line crossers represent a small percentage of observed overdose cases; however it is possible with both formulations (to a much lesser degree with IR)
- The modeling suggests that doses above 10 g are approximately the dose above which concentrations are expected to cross the nomogram line within 24 hours under fasting conditions without the influence of bezoar formation
- Patients who have taken an overdose of 25 and 50 g can experience prolonged elevated concentrations for 24 and 48 hours respectively or more for both the IR and MR formulations.
- Dosing with acetylcysteine within 8 hours for subjects that require it has been demonstrated to ensure survival and reduce the relative risk of hepatotoxicity
- Elimination half-life of greater than 4 hours has been associated with hepatotoxicity, while half-life greater than 5.5 hours providing even more discrimination. Moreover, observed concentrations greater than 2-3 times the

corresponding nomogram line value, have also been associated with hepatotoxicity. Late line crossers tend to have half-lives of greater than 4 hours or even ascending in the 4 – 8 hours timeframe.

- Even doses less than 10 g have resulted in late line crossing and toxicity with MR. Modeling has shown that prolonged and delayed absorption may contribute to this.
- Although massive overdoses (>30g) can currently be successfully managed by careful monitoring of clinical presentation and laboratory measures, there is opportunity to refine and optimize the utilization of acetylcysteine in these cases.

The above data suggest that initiating treatment with antidote as soon as possible after ingestion of a potential overdose is important in mitigating the toxicity of paracetamol overdose. It also suggests than in the past, it has been possible to miss or delay treatment due to low concentrations within the designated sampling window subsequently elevating. The modeling suggests that on a pharmacokinetic basis, the first dose level at which one can expect concentrations above the nomogram level is a 10 g acute ingestion; however, this is expected to occur outside of the designated 4 – 8 hour sampling time window. These points highlight the importance of establishing a minimum dose threshold above which treatment should be started immediately. This can also be applied to situations where time of ingestion, dose, or formulation are not known.

Based on an analysis of the pharmacovigilance data, the paradigms for management of paracetamol overdose in Denmark, Sweden, and Australia/New Zealand are efficient for identifying and treating the great majority of cases.

Importantly, the above observations appear to validate many of the important assumptions and principles behind the treatment paradigm for paracetamol poisoning in Australia and New Zealand. Namely, that overdoses above 10 g should be treated immediately without waiting for results from paracetamol concentration analysis. Moreover, where dose, time of ingestion, or formulation are not known, the same strategy should be applied while continuing to monitor the subject for signs of hepatic injury and paracetamol concentrations. Monitoring and treatment should continue until normalization of liver function tests and paracetamol concentrations. Nomograms that rely solely on the transgression of threshold paracetamol levels have been observed to delay treatment of antidote where they would have been initiated more promptly with a minimum dose level. At the 10 g overdose level, the risk of treating with acetylcysteine is outweighed by the benefit.]

Hi there

I wish to support fully the submission for the reclassification of melatonin.

I have analysed the risks associated with melatonin use in the past and have not been able to identify any substantive causes for concern at the doses proposed.

The original classification was a decision based medico-politics, not substantive evidence.

A decision to not amend the classification of melatonin will be further evidence of the inappropriateness of Medically minded regulators to regulate low risk natural health products.

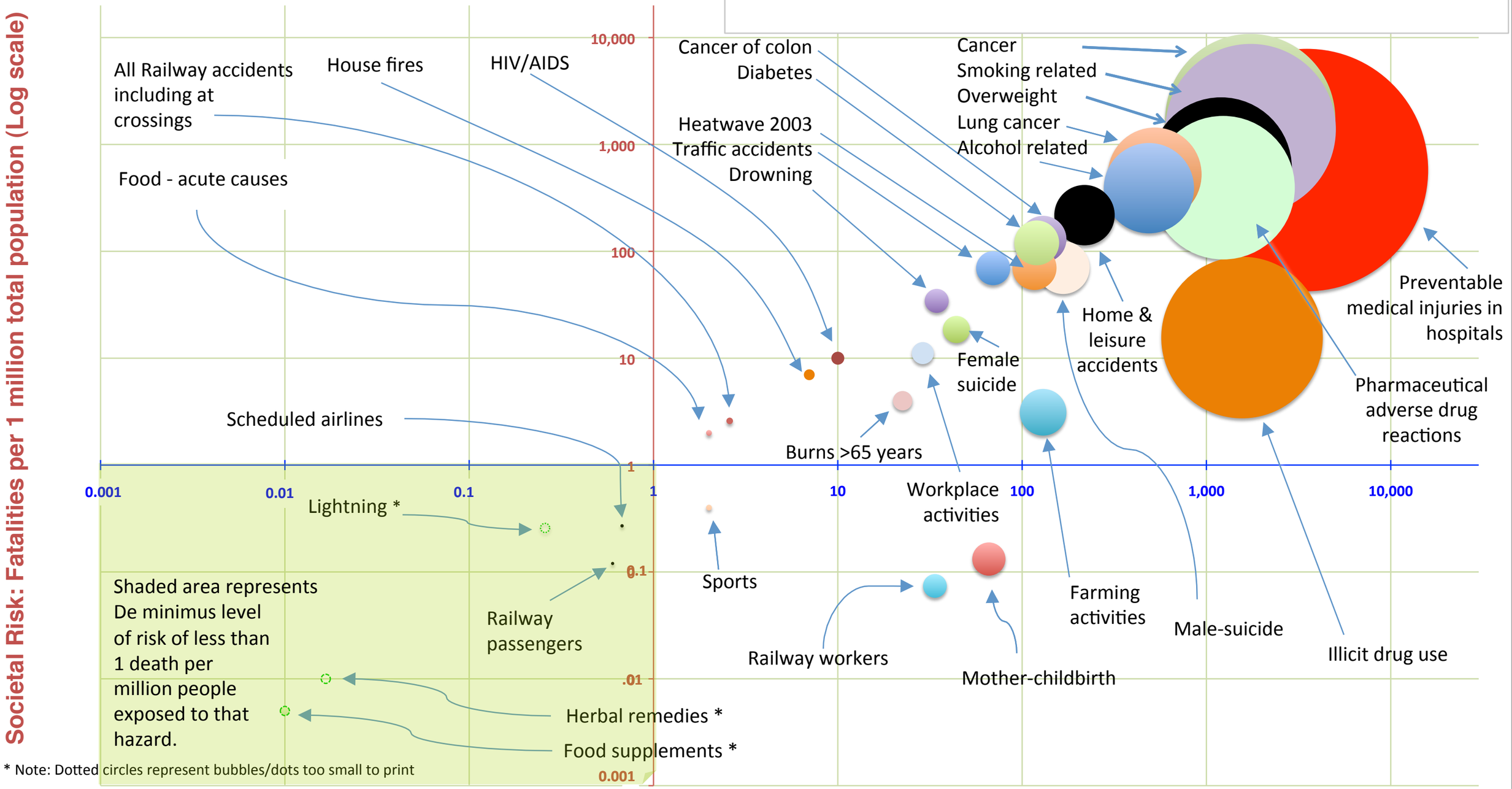
Natural health products have an incredibly safe risk-profile. Please see attached info graphics which include melatonin with the CM/NHP/DS categories which are to form part of this submission to the committee.

Regards

Ron Law
Risk & Policy Adviser

Societal vs Individual Risk of Death in Europe

Societal risk is represented as the risk of death per million total population.
Individual risk is represented as the risk of death per million exposed to a particular hazard. Bubble size represents the relative risk to an individual. By way of example, the bubbles representing deaths due to smoking exposure and illicit drug use are a similar size because the risk of death due to exposure to smoking is similar to that for an illicit drug user. Smoking poses a greater risk to society simply because vastly more citizens die due to exposure to smoking than illicit drug use.
Note: Log scales.



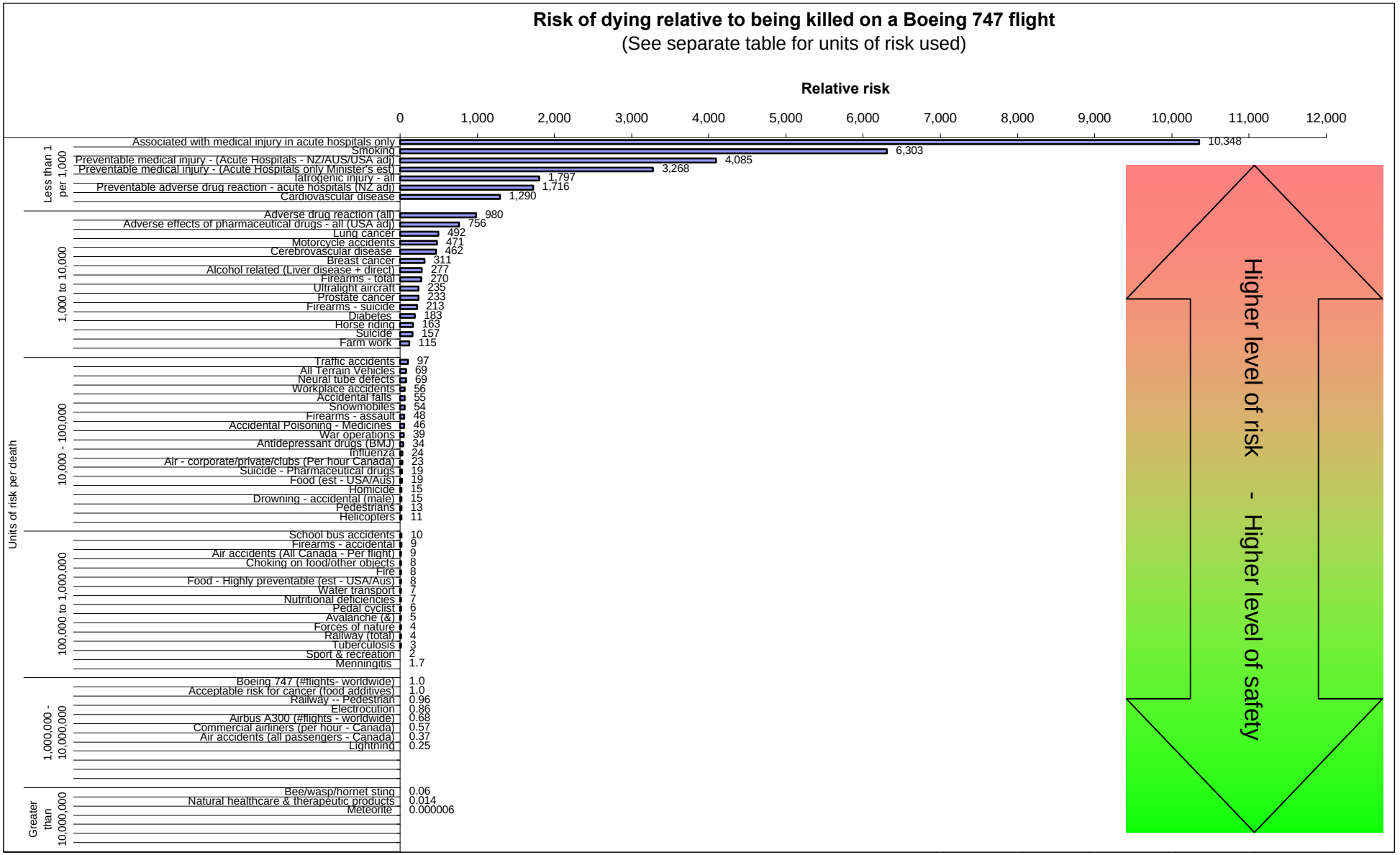
* Note: Dotted circles represent bubbles/dots too small to print

Sources: Variety of EC, EU27 Government and NGO databases, reports, officials and expert advisers including personal communitions requesting information from 75 EU advisers.

Commissioned by Alliance for Natural Health International (www.anhinternational.org)
Funding by Neal's Yard Remedies (www.nealsyardremedies.com)

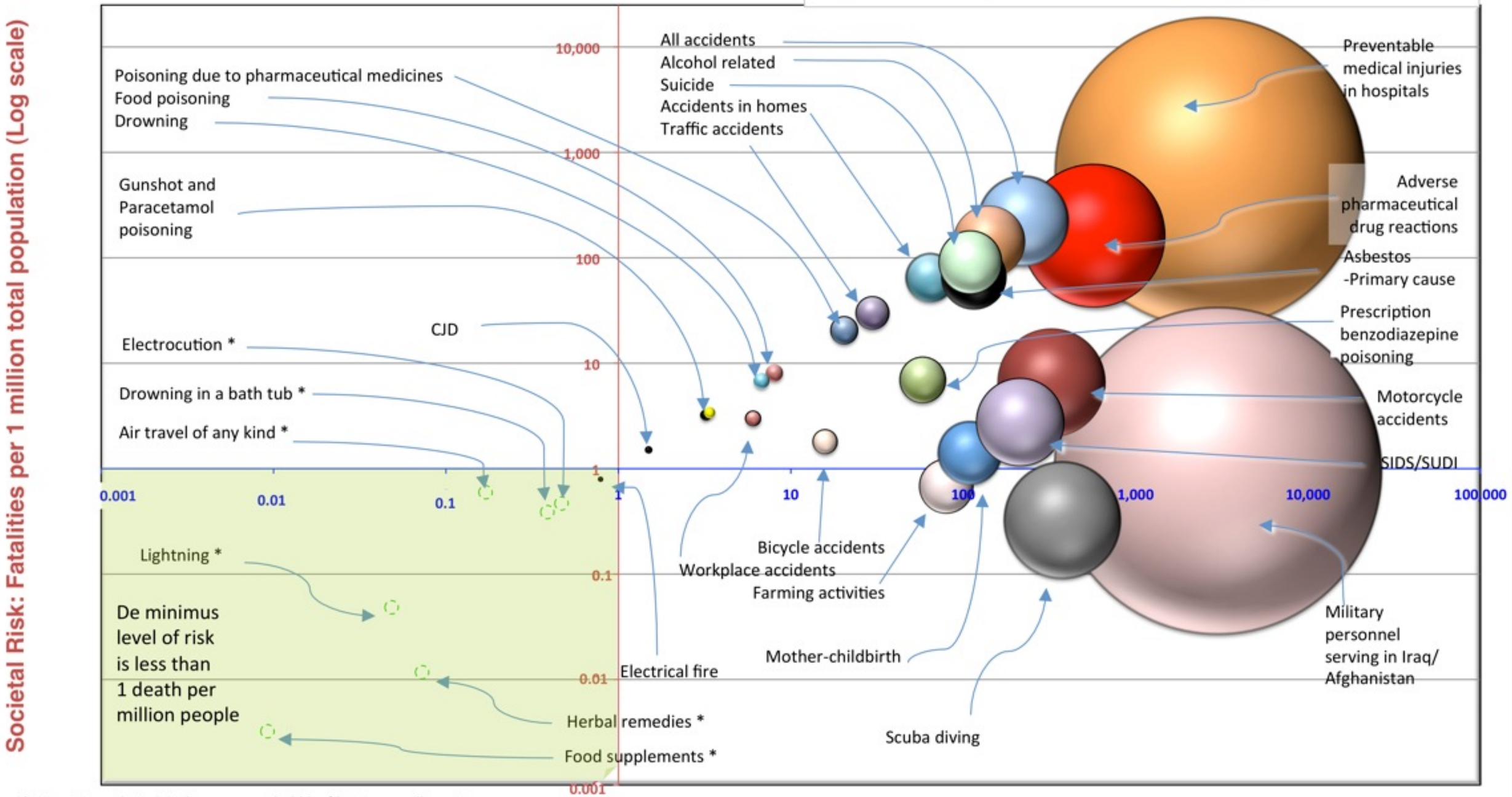
v2

Individual Risk: Fatalities per 1 million people exposed to risk (Log scale)


Risk of dying relative to being killed on a Boeing 747 flight
(See separate table for units of risk used)
Relative risk
0
1,000
2,000
3,000
4,000
5,000
6,000
7,000
8,000
9,000
10,000
11,000
12,000
Units of risk per death
Less than 1 per 1,000
1,000 to 10,000
10,000 - 100,000
100,000 to 1,000,000
1,000,000 - 10,000,000
Greater than 10,000,000
Associated with medical injury in acute hospitals only 10,348
Smoking 6,303
Preventable medical injury - (Acute Hospitals - NZ/AUS/USA adj) 4,085
Preventable medical injury - (Acute Hospitals only Minister's est) 3,268
Iatrogenic injury - all 1,797
Preventable adverse drug reaction - acute hospitals (NZ adj) 1,716
Cardiovascular disease 1,290
Adverse drug reaction (all) 980
Adverse effects of pharmaceutical drugs - all (USA adj) 756
Lung cancer 492
Motorcycle accidents 471
Cerebrovascular disease 462
Breast cancer 311
Alcohol related (Liver disease + direct) 277
Firearms - total 270
Ultralight aircraft 235
Prostate cancer 233
Firearms - suicide 213
Diabetes 183
Horse riding 163
Suicide 157
Farm work 115
Traffic accidents 97
All Terrain Vehicles 69
Neural tube defects 69
Workplace accidents 56
Accidental falls 55
Snowmobiles 54
Firearms - assault 48
Accidental Poisoning - Medicines 46
War operations 39
Antidepressant drugs (BMJ) 34
Influenza 24
Air - corporate/private/clubs (Per hour Canada) 23
Suicide - Pharmaceutical drugs 19
Food (est - USA/Aus) 19
Homicide 15
Drowning - accidental (male) 15
Pedestrians 13
Helicopters 11
School bus accidents 10
Firearms - accidental 9
Air accidents (All Canada - Per flight) 9
Choking on food/other objects 8
Fire 8
Food - Highly preventable (est - USA/Aus) 8
Water transport 7
Nutritional deficiencies 7
Pedal cyclist 6
Avalanche (&) 5
Forces of nature 4
Railway (total) 4
Tuberculosis 3
Sport & recreation 2
Meningitis 1.7
Boeing 747 (#flights- worldwide) 1.0
Acceptable risk for cancer (food additives) 1.0
Railway -- Pedestrian 0.96
Electrocution 0.86
Airbus A300 (#flights - worldwide) 0.68
Commercial airliners (per hour - Canada) 0.57
Air accidents (all passengers - Canada) 0.37
Lightning 0.25
Bee/wasp/hornet sting 0.06
Natural healthcare & therapeutic products 0.014
Meteorite 0.000006
Higher level of risk - Higher level of safety

Societal vs Individual Risk of Death in the United Kingdom

Societal risk is represented as the risk of death per million total population.
Individual risk is represented as the risk of death per million exposed to that hazard.
Bubble size represents the relative risk to an individual. By way of example, the bubbles representing deaths due to preventable medical injuries in hospitals and military personnel in Iraq/ Afghanistan are a similar size because the risk of death to a patient in a UK hospital is similar to that for a soldier deployed to a war zone. Medical injury poses a greater risk to society simply because vastly more citizens are exposed to that risk and hence die. **Note: Log scales.**



* Note: Green dotted circles represent bubbles/dots too small to print

v3

Sources: Variety of UK Government and NGO databases, reports, officials and expert advisers.

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Individual Risk: Fatalities per 1 million people exposed to risk (Log scale)

How Safe is Safe Enough?