From the Chief Medical Officer
Dr Michael McBride

Department of
Health, Social Services and Public Safety
www.dhsspsni.gov.uk

URGENT COMMUNICATION

HSS(MD)40/2012

For Action:
Chief Executives HSC Trusts
Medical Directors of HSC Trusts
(*for distribution to:*
Consultants in Emergency Medicine,
Intensive Care
all Acute Medical specialities
Paediatrics)

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Your Ref:
Our Ref: HSS(MD)40/2012
Date: 4 September 2012

Dear Colleague

PARACETAMOL OVERDOSE: NEW GUIDANCE ON USE OF INTRAVENOUS ACETYLCYSTEINE – ACTION REQUIRED

I am writing to inform you of important new guidance on the use of acetylcysteine for the treatment of acute paracetamol poisoning.

The Commission on Human Medicines (CHM) has reviewed the use of acetylcysteine for the treatment of acute paracetamol overdose and made the following recommendations:

- The licensed indication for acetylcysteine is now:
  - Paracetamol overdose irrespective of the plasma paracetamol level in circumstances where the overdose is staggered or there is doubt over the time of paracetamol ingestion; or
  - Paracetamol overdose with a timed plasma paracetamol concentration on or above a single treatment line joining points of 100 mg/L at 4 hours and 15 mg/L at 15 hours nomogram (see Annexe I), regardless of risk factors of hepatotoxicity.
- An increase in the duration of administration of the first dose of intravenous acetylcysteine from 15 minutes to 1 hour.
- Removal of hypersensitivity as a contraindication to treatment with acetylcysteine.
- Provision of a Technical Information Leaflet (TIL) for healthcare professionals in every pack of acetylcysteine, which gives more detailed instructions on the preparation of acetylcysteine infusions for administration.

The new indication should be used with immediate effect. The BNF will carry the new advice from September 2012 and other communications will support the change.

Further information is provided in the attached letter and on the MHRA website:
www.mhra.gov.uk/Safetyinformation/Safetywarningsalertsandrecalls/Safetywarningsandmessagesformedicines/CON178225

For further information on the changes to the prescribing information please see the information from the Commission on Human Medicines attached at (**ANNEX A)**.

Please report suspected adverse reactions to any medicine or vaccine through the Yellow Card Scheme:
https://yellowcard.mhra.gov.uk/

Yours sincerely

DR MICHAEL McBRIDE
Chief Medical Officer

For information:
Chief Executive, Health and Social Care Board
Chief Executive, Public Health Agency
Executive Medical Director/Director Public Health, Public Health Agency
Director of Integrated Care, Health and Social Care Board
Director of Nursing, Public Health Agency
Mr Joe Brogan, Asst Dir of Commissioning, Pharmacy & Medicines Management, HSC Board
Directors of Nursing, HSC Trusts
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Family Practitioner Service Leads, HSC Board
Professor Patrick Johnston, Dean, School of Medicine, Dentistry & Bio-medical Sciences, QUB
Dr Clare Loughrey, NIMDTA
Professor Linda Johnston, Head of School of Nursing & Midwifery, QUB
Dr Owen Barr, Head of School of Nursing, University of Ulster
Regional Medicines and Poisons Information Service, Belfast HSC Trust

This letter is available on the DHSSPS website at
www.dhsspsni.gov.uk/index/phealth/professional/cmo_communications.htm

COMMISSION ON HUMAN MEDICINES
CHAIRMAN: SIR GORDON W. DUFF

03 September 2012

Dear Colleague,

Paracetamol overdose: new guidance on use of intravenous acetylcysteine

Summary
The Commission on Human Medicines (CHM) has reviewed the use of acetylcysteine for the treatment of acute paracetamol overdose and made the following recommendations

- The licensed indication for acetylcysteine is now:
  - Paracetamol overdose irrespective of the plasma paracetamol level in circumstances where the overdose is staggered or there is doubt over the time of paracetamol ingestion; or
  - Paracetamol overdose with a timed plasma paracetamol concentration on or above a single treatment line joining points of 100 mg/L at 4 hours and 15 mg/L at 15 hours nomogram (see Annexe I), regardless of risk factors of hepatotoxicity.
- An increase in the duration of administration of the first dose of intravenous acetylcysteine from 15 minutes to 1 hour.
- Removal of hypersensitivity as a contraindication to treatment with acetylcysteine.
- The provision of weight-based acetylcysteine dosing tables for adults and children.
- Provision of a Technical Information Leaflet (TIL) for healthcare professionals in every pack of acetylcysteine, which gives more detailed instructions on the preparation of acetylcysteine infusions for administration (see Annexe II).

The list of products affected is attached at Annexe III.

Background
These changes are intended to simplify treatment decisions and reflect the findings of the CHM, that the evidence base to support the practice of risk factor assessment was poor and inconsistent, and that many of the risk factors were imprecise and difficult to determine with sufficient certainty in clinical practice. By removing the need to assess risk factors for hepatotoxicity, the approved indication for acetylcysteine is greatly simplified to a single treatment line on the paracetamol treatment nomogram. A substantial number of spontaneous reports of administration errors with intravenous acetylcysteine were also considered, some of which had the potential to cause significant harm. CHM recommends a range of risk minimisation measures to reduce the incidence of administration errors, most notably the introduction of weight-based dosage tables to remove the need to calculate the dose.

Further details about the CHM recommendations can be found on the MHRA website (http://www.mhra.gov.uk/Safetyinformation/Safetywarningsalertsandrecalls/Safetywarningsandmessagesformedicines/CON178225).

Timing
The new indication should be used with immediate effect. The BNF will carry the new advice from September 2012 and other communications will support the change.

CORRESPONDENCE TO: SECRETARY OF COMMISSION, S. SINGH, FLOOR 4.T
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Reporting suspected adverse drug reactions with the use of acetylcysteine
The MHRA is keen to monitor the impact of this change on patterns of adverse drug reactions linked to acetylcysteine. Serious adverse reactions to acetylcysteine should be reported to MHRA through the Yellow Card Scheme online at www.mhra.gov.uk/yellowcard.

Alternatively, prepaid Yellow Cards for reporting are available:

- upon request by mail: "FREEPOST YELLOW CARD"
- at the back of the British National Formulary (BNF)
- by telephoning the Commission of Human Medicines (CHM) free phone line: 0800 731 6789
- or by electronic download through the MHRA website (www.mhra.gov.uk/yellowcard)

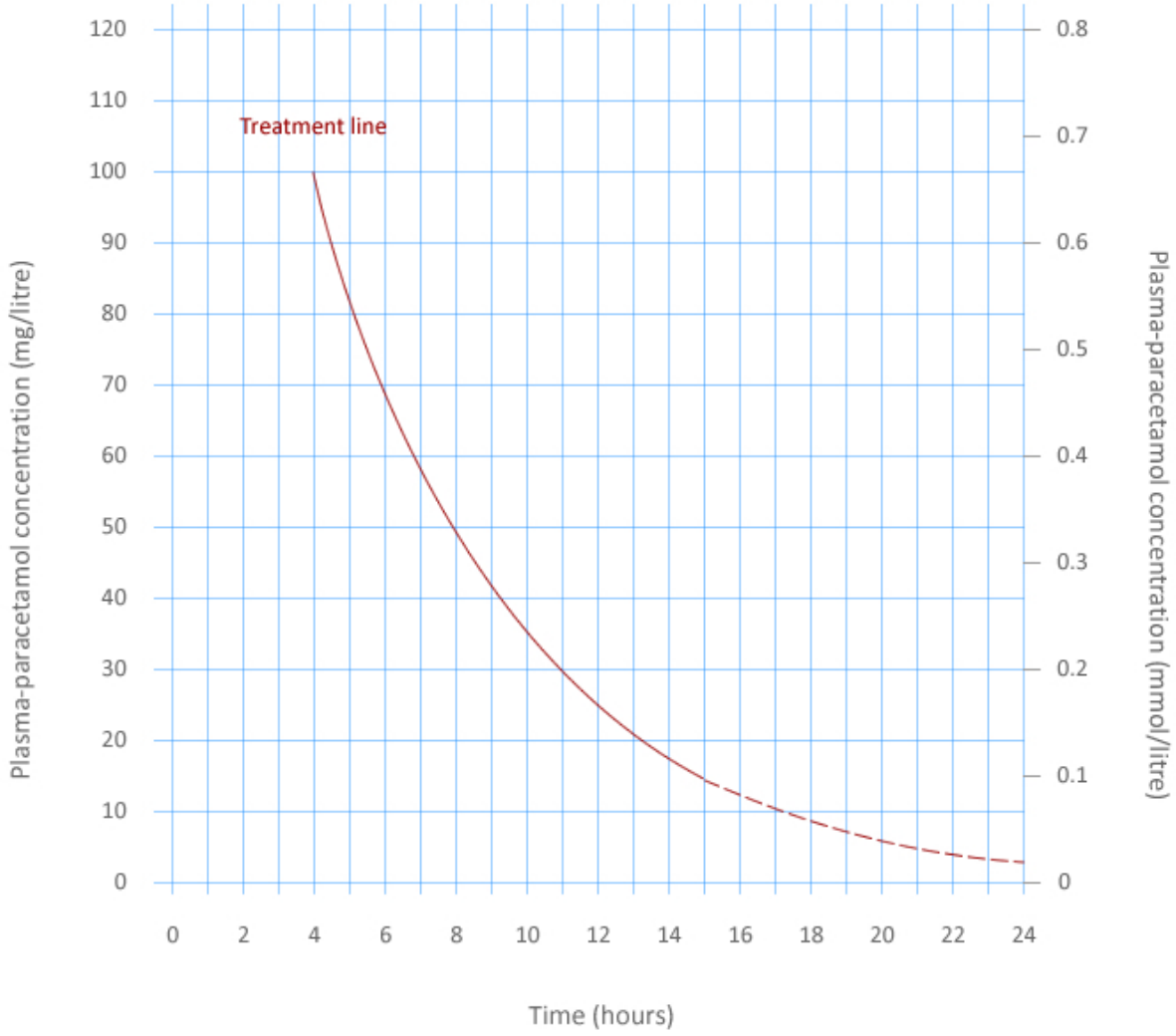
When reporting please provide as much information as possible, including information about medical history, any concomitant medication, onset and treatment dates.

Further information
For further information on this advice please contact the MHRA Information Centre on 020 7084 2000, email info@mhra.gsi.gov.uk, web address http://www.mhra.gov.uk.

Yours faithfully,

Professor Sir Gordon Duff,
Chairman, Commission on Human Medicines

Annexe I – Revised paracetamol overdose treatment nomogram



ACETYLCYSTEINE 200mg/mL INJECTION FOR INFUSION
ADMINISTRATION INFORMATION FOR THE HEALTHCARE PROFESSIONAL

Acetylcysteine should be administered by intravenous infusion preferably using Glucose 5% as the infusion fluid. Sodium Chloride 0.9% solution may be used if Glucose 5% is not suitable.

The full course of treatment with acetylcysteine comprises of 3 consecutive intravenous infusions. Doses should be administered sequentially with no break between the infusions. The patient should receive a total dose of 300 mg/kg body weight over a 21 hour period.

Adults

- Weigh the patient to determine the correct weight band.
- Use the adult dosage table to determine the appropriate volume of acetylcysteine (ampoule volume) to be added to the infusion fluid for each of the 3 infusion periods.

First infusion
Add the appropriate volume of acetylcysteine injection to 200 mL of infusion fluid and infuse over **1 hour**.

Second infusion
Add the appropriate volume of acetylcysteine injection to 500 mL of infusion fluid and infuse over the next **4 hours**.

Third infusion
Add the appropriate volume of acetylcysteine injection to 1 litre of infusion fluid and infuse over the next **16 hours**.

Adult Dosage Table

Adult acetylcysteine prescription (each ampoule = 200mg/mL acetylcysteine)					Please circle appropriate weight and volume.	
Regimen	**First Infusion**		**Second Infusion**		**Third Infusion**	
Infusion fluid	**200 mLs 5% glucose or sodium chloride 0.9%**		**500 mLs 5% glucose or sodium chloride 0.9%**		**1000 mLs 5% glucose or sodium chloride 0.9%**	
Duration of infusion	**1 hour**		**4 hours**		**16 hours**	
Drug dose	**150 mg/kg acetylcysteine**		**50 mg/kg acetylcysteine**		**100 mg/kg acetylcysteine**	
Patient Weight[1]	**Ampoule volume[2]**	**Infusion Rate**	**Ampoule volume[2]**	**Infusion Rate**	**Ampoule volume[2]**	**Infusion Rate**
kg	**mL**	**mL/h**	**mL**	**mL/h**	**mL**	**mL/h**
40-49	**34**	**234**	**12**	**128**	**23**	**64**
50-59	**42**	**242**	**14**	**129**	**28**	**64**
60-69	**49**	**249**	**17**	**129**	**33**	**65**
70-79	**57**	**257**	**19**	**130**	**38**	**65**
80-89	**64**	**264**	**22**	**131**	**43**	**65**
90-99	**72**	**272**	**24**	**131**	**48**	**66**
100-109	**79**	**279**	**27**	**132**	**53**	**66**
≥110	**83**	**283**	**28**	**132**	**55**	**66**

[1] Dose calculations are based on the weight in the middle of each band. If the patient weighs less than 40kg use the paediatric dosage table.
[2] Ampoule volume has been rounded up to the nearest whole number

Children

Children are treated with the same doses and regimen as adults. However, the quantity of intravenous fluid used has been modified to take into account age and weight, as fluid overload is a potential danger. Doses should be administered sequentially using an appropriate infusion pump.

Preparation and administration of paediatric infusions

- Weigh the child to determine the correct weight band.
- Read off the table the total infusion volume required for each dose according to the weight of the child and make up the solutions according to the directions below.

First Infusion

- Prepare a 50 mg/mL solution by diluting each 10 mL ampoule of acetylcysteine (200 mg/mL) with 30 mL glucose 5% or sodium chloride 0.9% to give a total volume of 40 mL.
- **Prepare the appropriate volume for the weight of the child**.
- The dose is infused over **1 hour** at the infusion rate stated in the table.

Second Infusion

- Prepare a 6.25 mg/mL solution by diluting each 10 mL ampoule of acetylcysteine (200 mg/mL) with 310 mL glucose 5% or sodium chloride 0.9% to give a total volume of 320 mL.
- **Prepare the appropriate volume for the weight of the child.**
- The dose is infused over **4 hours** at the infusion rate stated in the table.

Third Infusion

- Prepare a 6.25 mg/mL solution by diluting each 10 mL ampoule of acetylcysteine (200 mg/mL) with 310 mL glucose 5% or sodium chloride 0.9% to give a total volume of 320 mL.
- **Prepare the appropriate volume for the weight of the child.**
- The dose is infused over **16 hours** at the infusion rate stated in the table.

For example for a child weighing 12 kg, the first infusion would be 38 mL infused at 38 mL/h over 1 hour,the second infusion would be 100 mL infused at 25 mL/h over 4 hours and the third infusion is 208 mL infused at 13 mL/h over 16 hours.

Paediatric Dosage Table

Paediatric acetylcysteine prescription (each ampoule = 200mg/mL acetylcysteine)					Please circle appropriate weight and volume.	
Regimen	**First Infusion**		**Second Infusion**		**Third Infusion**	
Infusion	**50mg/mL for 1 hour**		**6.25mg/mL for 4 hours**		**6.25mg/mL for 16 hours**	
Infusion rate	**3mL/kg/h**		**2mL/kg/h**		**1mL/kg/h**	
Patient Weight[1]	**Total Infusion Volume**	**Infusion Rate**	**Total Infusion Volume**	**Infusion Rate**	**Total Infusion Volume**	**Infusion Rate**
kg	**mL**	**mL/h**	**mL**	**mL/h**	**mL**	**mL/h**
1	**3**	**3**	**8**	**2**	**16**	**1**
2	**6**	**6**	**16**	**4**	**32**	**2**
3	**9**	**9**	**24**	**6**	**48**	**3**
4	**12**	**12**	**32**	**8**	**64**	**4**
5	**15**	**15**	**40**	**10**	**80**	**5**
6	**18**	**18**	**48**	**12**	**96**	**6**
7	**21**	**21**	**56**	**14**	**112**	**7**
8	**24**	**24**	**64**	**16**	**128**	**8**
9	**27**	**27**	**72**	**18**	**144**	**9**
10-14	**38**	**38**	**100**	**25**	**208**	**13**
15-19	**53**	**53**	**140**	**35**	**288**	**18**
20-24	**68**	**68**	**180**	**45**	**368**	**23**
25-29	**83**	**83**	**220**	**55**	**448**	**28**
30-34	**98**	**98**	**260**	**65**	**528**	**33**
35-39	**113**	**113**	**300**	**75**	**608**	**38**

[1] Dose calculations are based on the weight in the middle of each band. If the patient weighs more than 40kg use the adult dosage table.
Figures have been rounded up to the nearest whole number

Annexe III – products affected

In the UK there are three licensed medicinal products containing acetylcysteine for intravenous administration:

PRODUCT	**MARKETING AUTHORISATION HOLDER**	**PL NUMBER**
Acetylcysteine 200 mg/mL injection	Aurum Pharmaceuticals Limited	PL 12064/0026
Acetylcysteine 200 mg/mL injection	Teva UK Limited	PL 00289/1543
Parvolex 200 mg/mL concentrate for solution for infusion	UCB Pharma Limited	PL 00039/0410