

## IN-USE PRODUCT SAFETY ASSESSMENT REPORT FOR INTRAVENOUS PARACETAMOL IN NEONATES, INFANTS AND CHILDREN.

### SUMMARY OF ASSESSMENT AND ITS FINDINGS

#### BACKGROUND

Intravenous paracetamol is used widely in neonatal, paediatric and adult settings and has become a baseline analgesic for many clinical procedures. It is available as a solution for infusion: 10mg/mL in 50mL vials and 100mL vials.(1-5)

In May 2010, the Medicines and Healthcare products Regulatory Agency (MHRA) issued a safety update to healthcare professionals in the UK highlighting the risk of accidental overdose of intravenous paracetamol in neonates, infants and children. (6) Similar concerns were also raised by the National Patient Safety Agency (NPSA). (7) The MHRA reported cases of accidental overdose in which confusion between the dose prescribed in mg and volume administered in mL had led to a 10-fold overdose. (6) The Safe Anaesthesia Liaison Group reported the possibility of accidental overdose in children associated with the use of 100mL vials. (8) To reduce the risk of errors the MHRA recommends the 50mL vial is restricted for use in neonates, infants and children who weigh less than 33kg (6); the 100mL vial would therefore be suitable for children, adolescents and adults weighing more than 33 kg. The manufacturers' product literature reflects these restrictions. (1-5) However despite this, adherence to these restrictions varies within the NHS.

More recently concerns have again been raised within the NHS on intravenous paracetamol products and the potential risk of confusion between the two volumes (50mL and 100mL) available from a single manufacturer, due to similarities in physical vial sizes and visual characteristics (see below for further detailed information). This review summarises practical in-use safety considerations associated with the use of intravenous paracetamol products. It also focuses on factors to consider in relation to safely picking the correct product prior to administration. The review has been produced following application of the validated UKMi product safety assessment tool (9), discussions with local ambulance teams and the Neonatal and Paediatric Pharmacy Group (NPPG).

#### DETAILS OF PRODUCT (S) ASSESSED

The following 10mg/mL intravenous paracetamol products were assessed using the validated UKMi product assessment tool. Only products available in both the 500mg (50mL) and 1g (100mL) volumes from a single manufacturer were assessed:

1. Paracetamol 500mg/50mL solution for infusion- manufactured by B. Braun Ltd
2. Paracetamol 1000mg/100mL solution for infusion – manufactured by B. Braun Ltd
3. Paracetamol 500mg/50mL solution for infusion- manufactured by Fresenius Kabi Ltd
4. Paracetamol 1000mg/100mL solution for infusion – manufactured by Fresenius Kabi Ltd
5. Perfalgan® (paracetamol) 10mg/mL solution for infusion; 50mL manufactured by Bristol-Myers Squibb Pharmaceuticals Ltd)
6. Perfalgan® (paracetamol) 10mg/mL solution for infusion; 100mL manufactured by Bristol-Myers Squibb Pharmaceuticals Ltd

Assessments were carried out with reference to: physical products (where available), high resolution images supplied by the manufacturers or various resources in the NHS, summaries of product characteristics (SmPCs). Photographic images are reproduced in Table 1 at the end of the report along with a summary of the assessment process.

#### CONCLUSION FOLLOWING APPLICATION OF VALIDATED ASSESSMENT TOOL

Potential risks are identified below; mitigating and other necessary actions are considered in the next section. A

comparison of the paracetamol products can be seen in Table 1 at the end of the report.

### Potential for confusion between products

The result of the risk assessment showed

- Overall all manufacturers distinguish between the different volumes by using different coloured sections on the product label. The total dose in mg is also presented on all the product labels; this is less prominent on the Bristol-Myers Squibb product compared to the other products.
- Fresenius Kabi products are particularly well differentiated due to the different colour vial caps.
- All manufacturers of the 50mL (500mg) vials state 'only for use in patients who weigh <33kg' on the product labels and for the 100mL (1000mg) vials state 'only for use in patients weighing more than 33kg' on the product labels
- B. Braun vials include all product information on one side of the vial therefore all the information is very easy to see without turning the vial around.
- Bristol-Myers Squibb and Fresenius Kabi products are further differentiated by the smaller vial size for the 50mL (500mg) product compared to the 100mL (1000mg) vial.
- All injectable medicines manufactured by B. Braun are packaged in the same Ecoflac® container therefore potentially making visual distinction between B Braun products or different volumes/strengths of the same product less obvious.

See table 1 for further information

### Risk of overdose

Paracetamol dosing in neonates, infants and children is weight dependent and usually very small volumes of paracetamol infusion are administered. The risk of overdose in this patient group is greater as a 50mL vial contains up to 10-20 times the dose required for neonates and infants e.g. a 2kg neonate requires a dose of 7.5mg/kg. A 15mg dose requires 1.5mL of the 50mL vial; inadvertent administration of the whole vial would result in a huge overdose. The size of the vial and the fact that it contains enough paracetamol to provide a dose suitable for all children up to 33kg makes it very difficult for practitioners to recognise errors, particularly for those not working in a neonatal or paediatric specific environment.

A lower volume paracetamol product is available in the UK, manufactured by B. Braun Ltd. This ampoule (10mg/mL) contains a total dose of 100mg (10mL) and more closely corresponds to the small volumes required for neonates, infants and children. Ideally all centres should be encouraged to use this product for neonates, infants or children <10kg. If this ampoule is used particular attention will be required to the storage of the product to reduce confusion with other small 10mL vials e.g. sodium chloride 0.9%, water for injection etc. Increased staff awareness and training on the availability of this product is also essential.



### POTENTIAL NEXT STEPS AND MITIGATION ACTIONS

Potential next steps and mitigation actions can be considered in two respects: those of particular relevance to the NHS (recommended practice and further actions to consider), and those of particular relevance to manufacturers.

#### To support safe use of intravenous paracetamol in neonates, infants and children, NHS organisations should:

1. Follow recommendations as outlined below to reduce accidental overdose:
  - a) Adhere to recommended dose as outlined in the BNF / BNFc.

- b) Be vigilant when prescribing and administering intravenous paracetamol to ensure that the correct dose is given, especially in neonates and infants where there is a risk of confusion due to prescription in mg and administration in mL. Prescribe the dose in mg not mL; confusion can result in a 10 fold overdose. (See section 2)
- c) Use the 50mL vial for neonates, infants and children who weigh less than 33kg and 100mL vial for patients weighing over 33kg.
- d) If patients require a volume less than the whole vial, withdraw the required dose into a syringe and administer from the syringe to reduce the risk of over infusion.
- e) Do not administer intravenous paracetamol concomitantly with oral paracetamol, including combination products.
- f) Where available, electronic systems should be used to their full potential to reduce errors.
  - Smart pumps: Syringe pump libraries should be built for paracetamol with defined limits to reduce the risk of a 10 fold dose being infused.
  - EPMA systems should be configured to prescribe paracetamol in mg with recommendations on the appropriate paracetamol vial size to use. It could also provide recommendations on syringe sizes to use. (See 2e below for further detail).

2. Consider these further actions:

- a) Review local analgesic prescribing policies to reduce the risk of accidental paracetamol overdose.
- b) Prescribe the dose in mg AND consider prescribing the total dose volume in mL to reduce any errors in calculation or confusion (Note this may not suit all settings; some hospitals have had errors with this recommendation. The success of this recommendation on preventing errors depends on many factors such as engagement of prescribers, experience of prescribers in the neonatal and paediatric setting, type of prescribing system and level of pharmacy cover etc. Therefore each setting should be risk assessed.)
- c) Consider stocking the B Braun 10mL (10mg/mL) ampoule, for use in children weighing <10kg. This product has been successfully used in neonatal and paediatric units in Kings College Hospital in London (10).
- d) Where purchasing contracts permit, consider using a different manufacturer for each specific volume (50mL and 100mL), in order to reduce picking errors.
- e) Use of a defined syringe size can be considered (but may not be suitable for all patient groups) to administer doses to neonates, infants and children of specific ages e.g. maximum 10mL syringe size for neonates.
- f) Use manufacturer educational Risk Minimisation Materials (see Links provided in table 1) to support safe use in neonates, infants and children.

#### **Further actions to be considered by manufacturers of Paracetamol infusions**

There have been considerable improvements made in the labelling of intravenous paracetamol products. Further recommendations include:

1. B. Braun to consider changing the physical size of the 50mL product to further differentiate between the two product volumes. Consider adding more colour to the product label and/or vial cap to create a clear visual difference between the products.
2. Bristol-Myers Squibb to improve labelling so the total dose in mg is clear on both vials
3. Manufacturers are encouraged to include all their risk management material on the Electronic Medicines Compendium [www.medicines.org.uk/emc](http://www.medicines.org.uk/emc) as well as their own company website.

This report was produced in May 2018 using photographic images and physical products of licensed intravenous paracetamol preparations available in both the 500mg (50mL) and 1g (100mL) size from a single manufacturer at the time of assessment. Images were obtained primarily from pharmaceutical companies, but also from the Commercial Medicines' Unit PharmaQC database (<http://cmu.dh.gov.uk/medicines/pharmaqc-database/>) and from various sources within the NHS.

This report summarises product assessments undertaken by:  
London Medicines Information Service based at Northwick Park Hospital and South West Medicines Information and Training (SWMIT) based at UHBristol NHS Foundation Trust. We are also grateful for the

input of clinical specialists (Neonatal and Paediatric Pharmacy Group, regional QA and the London Ambulance Service) in completing this piece of work. For comments email [lnwh-tr.medinfo@nhs.net](mailto:lnwh-tr.medinfo@nhs.net)

The UKMI product safety assessment group would appreciate your views on the usefulness of this report. We have devised a short survey which we would appreciate you completing, it should take approximately 10 minutes to complete. Click the following link to complete the survey:

<https://www.surveymonkey.com/r/UKMiProductSafetyAssessments>.

## References

1. Bristol-Myers Squibb Pharmaceutical Limited. Summary of Product Characteristics. Perfalgan 10mg/mL solution for infusion. Revision of text: October 2014. Accessed via [www.emc.medicines.org.uk](http://www.emc.medicines.org.uk) on 06/04/2018.
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5. Personal communication. B. Braun Risk Management Material. Last updated May 2017.
6. MHRA Drug Safety Update. July 2010. Intravenous paracetamol (Perfalgan ▼): risk of accidental overdose. Accessed online via: <https://www.gov.uk/drug-safety-update/intravenous-paracetamol-perfalgan-risk-of-accidental-overdose>
7. NPSA Signal. October 2010. Overdose of intravenous paracetamol in infants and children. Accessed online via: <http://webarchive.nationalarchives.gov.uk/20171030125800/http://www.nrls.npsa.nhs.uk/resources/patient-safety-topics/medication-safety/?entryid45=83757>
8. Safe Anaesthesia Liaison Group. May 2013. Intravenous Paracetamol. Accessed via: <https://www.aagbi.org/sites/default/files/intravenousparacetamol.pdf>
9. UKMi Product Safety Assessment tool. Available at: <https://www.sps.nhs.uk/articles/ukmi-product-assessment-tool/>
10. Cavell GF. A safer presentation of intravenous paracetamol is available. European Journal of Hospital Pharmacy. Doi:10.1137/ejhpharm-2017-001425.

**Table 1: A comparison of paracetamol 500mg /50mL and 1g/100mL solution for infusion products**

Manufacturer	Product	Risk Minimisation Materials (RMM)	Nature of container	Comments on risk assessment and potential for confusion
Bristol - Myers Squibb Pharmaceuticals Ltd		<a href="https://www.medicines.org.uk/emc/rmm/96/Document">https://www.medicines.org.uk/emc/rmm/96/Document</a>	Glass vial	<ul style="list-style-type: none"> <li>• 50mL vial significantly smaller in size than 100mL, therefore good visual difference.</li> <li>• The total dose (500mg and 1g) is not prominent on the vial labels</li> <li>• Different colour labels for each vial size: pink writing for 50mL vial and green writing for 100mL vial.</li> <li>• Label on 50mL vial state 'only for use in patients who weigh &lt;33kg' and 100mL vials 'only for patients weighing more than 33kg'. Writing is small and on the left edge of the label which could be missed.</li> </ul>

<p>Fresenius Kabi</p>		<p>Available from the manufacturer – not readily available online.</p>	<p>Glass vial</p>	<ul style="list-style-type: none"> <li>• 50mL vial significantly smaller in size compared to 100 mL, therefore visual difference.</li> <li>• Different colours used product for each vial size: blue writing and vial lid for 50mL vial and red writing and vial lid for 100mL vial.</li> <li>• Product label on 50mL vial state 'only for use in patients who weigh &lt;33kg' and 100mL vials state 'only for patients weighing more than 33kg'</li> </ul>
<p>B. Braun</p>		<p>Available from the manufacturer – not readily available online. Manufacturer send to all buyers monthly but this only goes to the purchasing teams and may not be seen by frontline staff.</p>	<p>Plastic vial</p>	<ul style="list-style-type: none"> <li>• Both 50mL and 100mL vial are the same size</li> <li>• Different coloured sections on product labels for each volume: yellow strip for 50mL vial and orange strip for 100mL vial.</li> <li>• Product label on 50mL vial state 'only for use in patients who weigh &lt;33kg'. The 100mL vials states 'only for patients weighing more than 33kg'. This is written in the clear line of vision directly under the product concentration.</li> <li>• Full label visible at a glance and vial doesn't need to be turned around.</li> </ul>