

## NCCP Recommendation on Preparation of Reduced Dose BCG

### 1 Recommendation

Following consideration of the information presented below the National Prostate/ Urology Clinical Leads Group made the following recommendations:

- 1) A reduced dose of BCG is not advised when its preparation is from a single dose product which facilitates the required normal single dose of BCG as the dose cannot be accurately measured.
- 2) A clinician may proceed with a reduced dose at their own discretion on an individual patient basis.
- 3) Patients should be informed as to the unavoidable potential inaccuracy when a reduced dose of BCG is prepared.
- 4) Patient consent should be obtained following discussion with the patient.
- 5) Due care needs to be taken with regard to the safety considerations of withdrawing part of the single dose vial(1, 2).

### 2 Information considered by the National Prostate/ Urology Clinical Lead Group

#### 2.1 Background:

BCG (Bacillus Calmette Guérin) is a live attenuated strain of Mycobacterium bovis indicated for the treatment of non-muscle invasive bladder carcinoma.

As BCG carries a potential health risk to anyone exposed to it during handling, there are specific instructions for its reconstitution and handling (3).

This recommendation document is in relation to the preparation of BCG to facilitate a reduced dose (reduce to 1/3 dose) for patients experiencing adverse events (4, 5).

#### 2.2 Products available in Ireland

BCG-medac is the only licensed BCG available in Ireland<sup>1</sup>. There is only one strength of the product available which facilitates the required normal single dose of BCG. A reduced dose would require part of the product to be used.

This is a closed system product consisting of a vial of powder and solvent for the suspension of the powder for intravesical use, the entire contents are infused via a catheter into the patient's bladder. This product contains  $2 \times 10^8$  to  $3 \times 10^9$  viable units of BCG bacteria seed RIVM derived from seed 1173-P2.

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<sup>1</sup> Responses obtained from a 2018 survey by NCCP of Irish hospitals administering BCG for bladder cancer.

The use of a closed system reduces the risk of exposure to BCG when preparing the product for instillation.

### 2.3 Other products

There are a number of other BCG products indicated for the treatment of non-muscle invasive bladder carcinoma such as ImmuCyst<sup>®</sup>, Onco-TICE<sup>®</sup> and TheraCys<sup>®</sup>. These are not interchangeable with BCG-medac, nor are they licensed for use or available in Ireland.

These products are also only available as one strength which facilitates the required normal single dose of BCG. A reduced dose would require part of the product to be used.

### 2.4 Preparation area for administration

Currently BCG is prepared in the ward/theatre where it is to be administered<sup>1</sup>.

### 2.5 Information on preparation of a reduced dose

- Lamm protocol. TheraCys<sup>®</sup> 81mg is a freeze-dried preparation made from the Connaught strain of BCG containing  $10.5 \pm 8.7 \times 10^8$  colony-forming units (CFU) per vial when resuspended in the diluent provided. No information is provided regarding the measurement of the reduced dose(4).
- Nouhad et al URO-BCG 4 study used Immucyst<sup>®</sup> 80mg. Immucyst<sup>®</sup> is a freeze-dried preparation containing approximately  $1.8$  to  $15.9 \times 10^8$  Colony Form Units of the Connaught substrain of BCG (6). A reduced dose was prepared by using part of the reconstituted vial and diluting further to obtain a total of 50ml containing the 1/3 dose of BCG ready for intra bladder instillation (5).
- The National Medicines Information Centre found no information on their current literature databases on how reduced doses of BCG-medac could be prepared<sup>2</sup>.
- There are no recommendations for dose reductions of BCG-medac<sup>®</sup> in the Summary of Product Characteristics (SPC). Steps are recommended to deal with specific side effects that may require treatment with BCG-medac to be discontinued (1). The manufacturer does not recommend reduction of dosage of BCG-medac as there is no accurate way to measure a reduced dose. The company have advised that splitting the dose in the vial after reconstitution bears some risks due to technical issues such as aggregation of the bacteria<sup>3</sup>.

### 2.6 Preparation methods to prepare a reduced dose of BCG

- 1) Reconstitute the vial and measure a reduced dose by using part of a vial further diluted for instillation.
- 2) Reconstitute the vial and further dilute the entire dose. The reduced dose is achieved by instillation of the volume estimated to achieve the required dose. This would require a visual

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<sup>2</sup> National Medicines Information Centre, personal communication, May 16<sup>th</sup> 2018.

<sup>3</sup> Medac Medical Information: Therapeutic Area Urology, personal communication, May 22<sup>nd</sup> 2018.

assessment to determine when the estimated volume has been administered. In the case of 1/3 dose of BCG-medac this would result in a smaller volume (~ 17ml) being instilled rather than the recommended 50ml.

Both of these preparation methods are subject to the following uncertainties:

1. An unknown number of viable bacteria.
2. The aggregation of the suspended cells resulting in a suspension that is almost impossible to split evenly.

Note: The safety considerations of withdrawing part of the vial would also need consideration (1, 2).

All comments and feedback are welcome at [oncologydrugs@cancercontrol.ie](mailto:oncologydrugs@cancercontrol.ie)

### 3 References

1. Health and Safety Executive. Control of Substances Hazardous to Health (COSHH). 6 ed: HSE Books; 2013.
2. HSE. Guideline on the Safe Handling & Use of Cytotoxic Drugs. 2016.
3. BCG-medac Summary Product Characteristics. [www.HPRA.ie](http://www.HPRA.ie) [cited May 2018]. Available from: <https://www.medicines.org.uk/emc/product/1540/smhc>.
4. Lamm DL. Protocol for BCG + maintenance, Donald L. Lamm, MD - Bladder Cancer WebCafé. 2018.
5. Nouhaud FX, Rigaud J, Saint F, Colombel M, Irani J, Soulie M, et al. Final results of the phase III URO-BCG 4 multicenter study: efficacy and tolerance of one-third dose BCG maintenance in nonmuscle invasive bladder cancer. *Anticancer Drugs*. 2017;28(3):335-40.
6. ImmuCyst Summary Product Characteristics. [www.medicines.org.uk](http://www.medicines.org.uk) [cited May 2018]. Available from: <https://www.medicines.org.uk/emc/product/1540/smhc>.

Version	Date	Amendment	Approved By
1	01/06/2018		NCCP in consultation with National Prostate/ Urology Clinical Leads group