| | |
|---|---|
| **TITLE** | **COMPARATIVE EFFECTIVENESS AND SAFETY OF IPRAMOL (IPRATROPIUM/ALBUTEROL) STERINEBS® VS. DUONEB®** |
| Subtitle | Historic cohort, US database study comparing effectiveness and safety of nebulised COPD medication labelled by Teva Ltd (Ipramol SteriNebs®) against the originator product (DuoNeb®) |
| Protocol version identifier | v03 |
| Active substance | Ipratropium bromide and albuterol sulphate |
| Medicinal product | Ipramol (ipratropium/albuterol) SteriNebs® 0.5 mg/3 mg (equivalent to 2.5 mg of albuterol base) per 3 ml solution |
| Product code | NDC code: 0093-6723-73 (0.5 mg/3 ml, 2.5 mg/3 ml)<br>NDC code: 0093-6723-74 (0.5 mg/3 ml, 2.5 mg/3 ml) |
| Marketing authorisation holder | IVAX Pharmaceuticals<br>Ridings Point, Whistler Drive<br>Castleford<br>West Yorkshire<br>WF10 5HX<br>United Kingdom |
| Marketing category and application number | ANDA076724 |
| Research questions and objectives | To examine if nebulised medication labelled by Teva Ltd (Ipramol [ipratropium/albuterol] SteriNebs®) is non-inferior to (at least as effective and safe as) the originator product (DuoNeb®) |
| Country of study | USA |
| Author | RiRL<br>5 Coles Lane<br>Oakington, Cambridge<br>CB243BA<br>United Kingdom |

# TABLE OF CONTENTS

# 1. BACKGROUND AND RATIONALE

Teva Ltd is a global company ranking among the 10 top pharmaceutical companies in the world. Headquartered in Israel, Teva is active in 60 countries, with over 46,400 dedicated employees worldwide. The company is now looking to launch 3 different nebuliser products in China: Budesonide, Salbutamol and Ipramol (Ipratropium/Albuterol) SteriNebs®. This protocol focuses on Ipramol SteriNebs®.

Ipramol SteriNebs® is currently marketed in the United States of America (USA), Denmark, Finland, Germany, the Netherlands, Sweden, and the United Kingdom (UK), and is the generic

product of DuoNeb® (Combivent® in the UK), which is marketed worldwide, including China. Both products are nebuliser solutions indicated for the management of bronchospasm in patients suffering from chronic obstructive pulmonary disease (COPD).

The active ingredients in these drugs are ipratropium bromide and albuterol (salbutamol) sulphate. Ipratropium bromide is an anticholinergic bronchodilator, which blocks the muscarinic receptors of acetylcholine in an anticholinergic/parasympatholytic manner. Albuterol sulphate, a derivative of salbutamol, is a selective β2 adrenoreceptor agonist providing short-acting bronchodilation with a fast onset in reversible airways obstruction. Simultaneous administration of both an anticholinergic and a β2-sympathomimetic is designed to produce greater bronchodilation effects than when either drug is utilized alone at its recommended dosage.

In order to support a clinical trial waiver for marketing Ipramol SteriNebs® in China, Teva will provide recent data demonstrating their product is not inferior to the originator DuoNeb® (Combivent® in the UK). To accomplish this, an historic, cohort, data-base study will be conducted comparing effectiveness and safety of the usage of the two products in the USA, where Ipramol SteriNebs® is on the market since 2008. A regulatory standard protocol, together with the completed analysis will be provided for the submission to Chinese regulators.

## 2. AIM AND OBJECTIVES

The aim of this study is to compare Ipramol SteriNebs® with its originator, DuoNeb® (Combivent® in the UK). The primary objective is to assess whether effectiveness (in terms of COPD exacerbations) of Ipramol SteriNebs® is non-inferior to that of DuoNeb®. The secondary objective is to compare safety of Ipramol SteriNebs® vs DuoNeb®. In order to evaluate the regular usage of the two drugs, this study will look at COPD patients, however, patients with comorbid asthma will not be excluded.

# 3. DATA SOURCE AND EXTRACTION

This study will use the Clinformatics™ Data Mart (CDM) database (1) , an anonymous patient longitudinal database (APLD, US observational data), which contains retrospective claims data (2000-2012) from an employed, commercially insured United States population, including more than 45 million unique members. It is provided by Optum Life Sciences (2) and contains:

- Medical claims (primary care and secondary care)
- Pharmacy claims
- Laboratory results
- Pricing information

Data from this database will be obtained using an appropriate data-extraction algorithm, and will then be validated and cleaned for statistical analysis.

# 4. RESEARCH METHODS

## 4.1 Study products

- Reference Therapy**:** DuoNeb® (Combivent® in the UK)

Originator product consisting of a solution for inhalation via a nebuliser containing the short-acting β2-adrenergic agonist (SABA) albuterol (salbutamol) sulphate and the short acting muscarinic antagonist (SAMA) ipratropium bromide. A single dose is available in a 3 ml sterile solution for nebulisation in sterile low-density polyethylene unit-dose vials: ipratropium bromide 0.5 mg / albuterol (salbutamol) sulphate 3.0 mg (equivalent to 2.5 mg of albuterol base).

- Investigational Product**:** Ipramol SteriNebs®

Generic product of DuoNeb® (Combivent® in the UK). It is a solution for inhalation via a nebuliser containing the SABA albuterol (salbutamol) sulphate. A single dose is available in a 3 ml ampoule: ipratropium bromide 0.5 mg / albuterol (salbutamol) sulphate 3.0 mg (equivalent to 2.5 mg of albuterol base).

### 4.2 Study period

In order to include as many patients as possible, the study period will cover two years within a maximum period from January 2007 (one-year before the launch of Ipramol SteriNebs® in the US) up to the date of last available data.

### 4.3 Study design

This study will be designed as a matched historic, cohort, database study consisting of a baseline period, an index prescription date (IPD) and an outcome period (Fig.1).

The **baseline period** is a 1-year period before and including IPD[1] and is intended for patient characterization and confounder definition. The **IPD** is defined as the date (day/month/year) at which COPD patients who were not on SAMA/SABA nebulisers in baseline, initiated on either DuoNeb® or Ipramol SteriNebs®. Matching will be performed between the two initiation cohorts to ensure comparison of homogeneous groups of patients.

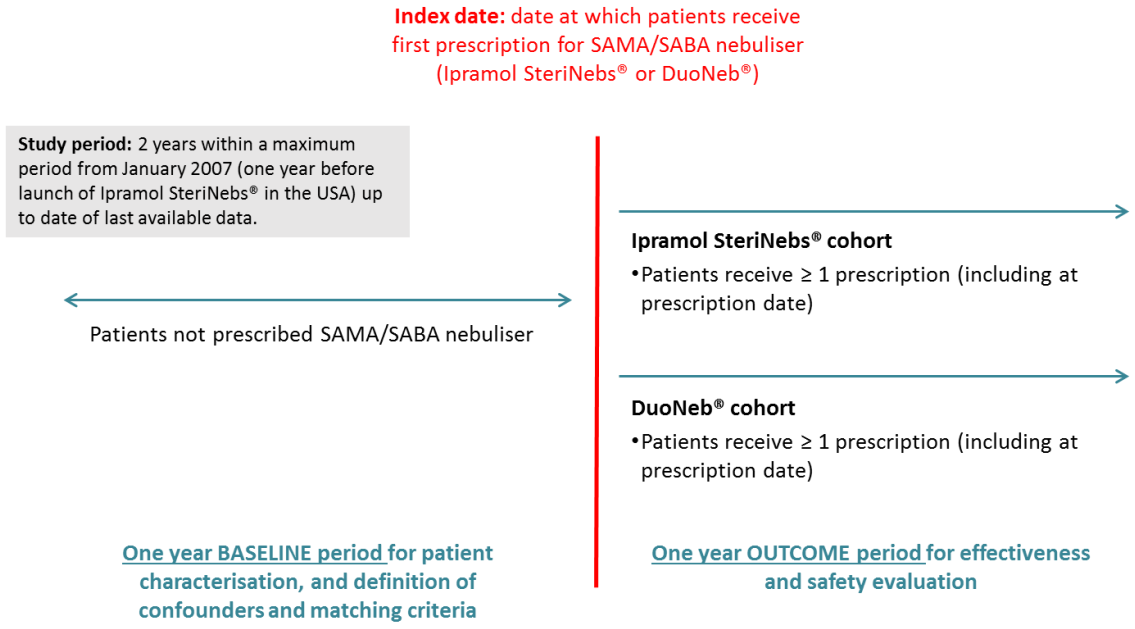


**Figure 1: Study design**

The **outcome period** is a 1-year period following IPD and will be used to compare drug effectiveness and safety.

[1] Except for therapy prescribed at IPD (which is included in the outcome).

One-year time periods for baseline and outcome are deemed necessary to record any measurable change in variables, and also to allow for seasonal changes in respiratory disease and its related conditions.

### 4.4 Study population

COPD patients will be included in the analysis if they meet the following criteria:

*Inclusion criteria*

- Aged ≥35 years at IPD
- ≥ 1 prescription for either Ipramol SteriNebs® or DuoNeb® at IPD
- At least two years of continuous data (1 year prior and 1 year post IPD)

*Exclusion criteria*

- Patients received a prescription for a SAMA/SABA nebuliser in the baseline period (1 year prior to IPD)

## 5. VARIABLES

### 5.1 Primary outcome

The primary outcome of this study is "effectiveness", evaluated in terms of:

- Severe COPD exacerbations (hospitalisations) in the outcome period
- Moderate and severe COPD exacerbations in the outcome period

Whereby[2]:

**Severe COPD exacerbations (hospitalisations)** is defined as:

- COPD-related[3] emergency department (ED) visits, OR
- COPD-related Inpatient admissions

**Moderate and severe COPD exacerbation** is defined as:

- Severe COPD exacerbation (hospitalisation; as defined above), OR

[2] Where ≥1 hospitalisation / oral steroid course / antibiotics prescription occur within 2 weeks of each other, these events will be considered to be the result of the same exacerbation and will only be counted once.
[3] Defined by one of the diagnostic codes for respiratory diseases included in Annex 1.

- An acute course of oral steroids[4] prescribed for a lower respiratory event[5], OR
- Antibiotics prescribed for a lower respiratory event

### 5.2 Secondary (exploratory) outcome

The secondary outcome of this study is "safety", evaluated in terms of Adverse Events (AEs).

Unique AEs are not identified in the CDM database. Instead pre-defined adverse terms can be identified and coded according to the Medical Dictionary for Regulatory Activities (MedDRA) standards. These will include AEs known to be related to Ipramol SteriNebs® and DuoNeb®, as specified in their respective summary of product characteristics. In order to do so, we will use ICD-9 Codes and convert them to MedDRA codes categorised by disease area (e.g. cardiovascular events, renal events). Data will be extracted on all adverse events, serious or otherwise.

### 5.3 Demographics and baseline variables

In order to capture real-world data on the utilisation of Ipramol SteriNebs® and DuoNeb® in clinical practice, the patients prescribed these therapies will be characterised according to their:

- Age at or nearest to IPD and sex
- Prior maintenance therapy (maintenance therapy prescribed before IPD)
- Baseline comedication (presence of a prescription of non-steroidal anti-inflammatory drugs [NSAIDs] and beta-blockers)
- Disease control in the year prior to IPD, defined as:
  - Number of COPD-related exacerbations (severe and moderate/severe)
  - Prescriptions for acute oral steroids or antibiotics for treating exacerbations
  - Reliever medication usage
- Comorbidities (presence of comorbid diagnoses, also using the Charlson Comorbidity Index)

[4] Defined as all courses where dosing instructions suggest exacerbation treatment (e.g. 6,5,4,3,2,1 reducing, or 30mg as directed) and/or all courses unlikely to be maintenance therapy (i.e. with no dosing instructions but recorded within a ±5-day window from a lower respiratory event).

[5] Defined as either a COPD-related ED visit / hospital admission / ambulatory visit or a respiratory investigation recorded within a ±5-day window from the prescription. A respiratory investigation comprises one of the following clinical procedures: chest radiograph (x-ray), chest computerised tomography (CT) scan, bronchogram, pneumogram, chest sonogram, lung biopsy and bronchoscopy.

# 6. STATISTICS

Analyses will be carried out using SPSS Statistics 21 (IBM SPSS Statistics, UK) and SAS 9.3 (SAS Institute, UK) software.

## 6.1 Power calculation

A previous RiRL study has reported that 40.8% of COPD patients (2,730 out of 6,687 patients) using Salbutamol inhalers have at least one exacerbation in the period of 1 year after initiation.[6] Assuming the proportion in the standard group is 40% and an expected difference between the proportions is 0.000, the sample size required to adequately power the study in a two-group large-sample normal approximation, with a one-sided 0.050 significance level, based on a 3:1 ratio of patient selection is 536 for the Ipramol SteriNebs® group and 1,606 for the DuoNeb® group. This enables 80% power to reject the null hypothesis that the investigational and the reference treatment are not equivalent (where the acceptable difference is 6.1% [i.e. 15% of 40.8%]). (3)

A mixed matching of 1:1, 2:1 and 3:1 will be adopted to maintain overall power at 80% due to the low numbers expected after applying inclusion/exclusion criteria (Table 1). A separate subgroup of 3:1 matches only will be analysed with power calculated to be 73% in this group.

| Study drugs | NDC codes | Strength | Launch date | Patients |
|---|---|---|---|---|
| **Ipratropium/Albuterol SteriNebs® (Teva USA)** | 0093-6723-73 | 0.5 mg/3 mL, 2.5 mg/3 mL | 02/01/2008 | **1,317** |
| | 0093-6723-74 | 0.5 mg/3 mL, 2.5 mg/3 mL | 02/01/2008 | |
| **DuoNeb® (Dey Pharma)** | 49502-672-30 | 0.5 mg/3 mL, 3 mg/3 mL | 15/02/2011 | **9,420** |
| | 49502-672-60 | 3 mg/3mL, 0.5 mg/3mL | 15/02/2011 | |

Table 1. Preliminary numbers for patients with at least one prescription for the study drugs (from Clinformatics™ Data Mart).

## 6.2 Exploratory analysis

Prior to the extended statistical analysis, an exploratory analysis of each cohort will be carried out for data validation and to identify potential outliers. The exploratory analysis will also help to investigate possible baseline differences between the two treatment groups in order to

[6] Data presented at annual scientific meeting of the American College of Allergy, Asthma and Immunology (ACAAI), November 7-11, 2013, Baltimore, USA.

evaluate whether the analysis may benefit from matching on these variables. Unmatched/matched statistical analyses will be performed using appropriate regression modelling. This robust statistical approach minimizes potential confounding of results by indication or severity. Statistically significant results will be defined as $p<0.05$ and trends as $p<0.10$.

### 6.3 Summary statistics

Summary statistics will be produced for all baseline and outcome variables by treatment groups, including:

(1) Variables measured on the interval/ratio scale:

- Sample size (n) and percentage non-missing
- Mean and Variance / Standard Deviation
- Range (Minimum / Maximum)
- Median and Inter-quartile Range (25th and 75th percentiles)

(2) Categorical variables:

- Sample size (n)
- Range (if applicable)
- Count and Percentage by category (distribution)

### 6.4 Comparisons between treatment arms

Treatment arms will be compared using the following tests:

(1) Variables measured on the interval/ratio scale:

- t-test (normal distribution)
- Mann-Whitney U test (skewed data)

(2) Categorical variables:

- Chi square test

### 6.5 Patient matching

If necessary depending on baseline results, individual patients in the two treatment groups (i.e. DuoNeb® or Ipramol SteriNebs®) will be matched to ensure the comparison of like patients. All patients satisfying inclusion and exclusion criteria in the DuoNeb® study cohort are considered as potential 3:1 matches to Ipramol SteriNebs® patients. The final selection of matched patients will ensure that only unique patients are selected from all cohorts by random methods. Random selection process through SAS statistical software will be used to

avoid selection bias. The matching criteria and matching ratio for each patient will be determined once the baseline data are examined. Baseline characterisation will be via demographics and clinical variables (for example age, sex, baseline exacerbations, acute oral steroid use or maintenance therapy during baseline). Any residual differences between the treatment groups after matching that are considered to be potentially significant ($p<0.10$) and any variables predictive of the outcome will be adjusted for through further statistical modelling. When variables are colinear in nature, clinical input will be sought to decide which of those that are colinear are put into the model.

### 6.6 Comparisons between effectiveness outcomes (primary analyses)

1. Severe COPD exacerbation (hospitalisation) rate

Severe COPD exacerbations (hospitalisations) in the outcome period will be compared between treatment groups using a conditional Poisson regression model. The model will use empirical standard errors (for more conservative confidence interval estimations) and adjustments will be made for potential baseline confounders. The adjusted rate ratio with 95% confidence interval will be reported.

2. Moderate and severe COPD exacerbation rate

Moderate and severe COPD exacerbations in the outcome period will be compared between treatment groups using a conditional Poisson regression model. The model will use empirical standard errors (for more conservative confidence interval estimations) and adjustments will be made for potential baseline confounders. The adjusted rate ratio with 95% confidence interval will be reported.

Baseline characterisation will be used to adjust for confounding factors. Variables that are found to be significantly different or show a trend towards a difference ($p < 0.10$) between the treatment groups at baseline will be included as potential confounding factors. In addition, variables that are found to be predictive ($p < 0.05$) of the outcome through multivariate analysis will also be considered as potential confounders.

### 6.7 Comparisons among safety variables (secondary/exploratory analyses)

AE rates (as total and individual events) in the outcome period will be compared between treatment groups using a conditional Poisson regression model. The model will use empirical standard errors (for more conservative confidence interval estimations), and adjustments will

be made for potential baseline confounders. The adjusted rate ratio with 95% confidence interval will be reported.

## 7. LIMITATIONS OF RESEARCH METHODS

As with all database studies, a number of limitations exist for which it is not possible to adjust (e.g. potential confounding factors with the problem of internal validity).

The methods of adjustment described in the Study Design will be used to address all factors for which it is possible to account for. Given the inherent limitations of database studies, however, the study results need to be viewed in conjunction with those from other studies, in particular randomised controlled trials.

## 8. PROTECTION OF HUMAN SUBJECTS

Due to the sensitive nature of personal medical data, all the researchers involved in this study are aware of ethical and regulatory aspects and strive to take all reasonable measures to ensure compliance with ethical and regulatory issues on privacy. The CDM database used for this study is already used for Pharmacoepidemiological research (4-6) and has a well-developed mechanism to ensure that regulations dealing with ethical use of the data and adequate privacy controls are adhered to.

## 9. REGULATORY AND ETHICAL COMPLIANCE

This study was designed and shall be implemented and reported in accordance with the criteria of the "European Network Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) studies" and follows the ENCePP Code of Conduct (EMA 2014) (7).

## 10. DISSEMINATION PLAN

This study will be registered with ENCePP with the aim of presenting initial results in poster/oral format at appropriate thoracic conferences. At least one manuscript containing more detailed results and methodology will be submitted to a journal specialising in respiratory medicine. Submission for publications should be made as soon as the analyses are

completed and the results are verified. Preferred respiratory congresses and journals will be agreed in discussion with Teva Ltd.

## 11. STUDY TEAM

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Senior Statistician: Annie Burden (annie@rirl.org)

Project Lead Statistician: Vicky Thomas (vicky@rirl.com)

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Project Research Lead: Rafael Mares (rafael@rilrl.com)

**Study Sponsor**:

Teva Pharmaceuticals Ltd.

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## 12. REFERENCES

(1) Clinformatics™ Data Mart (CDM) database. www.optum.com

(2) Optum Life Sciences (provider of CDM. www.optuminsight.com

(3) Price D, Small I, Haughney J, Ryan D, Gruffydd-Jones K, Lavorini F, Harris T, Burden A, Brockman J, King C, Papi A. Clinical and cost effectiveness of switching asthma patients

from fluticasone-salmeterol to extra-fine particle beclometasone-formoterol: a retrospective matched observational study of real-world patients. Prim Care Respir J. 2013; 22(4):439-48.

(4) Oleen-Burkey M, Cyhaniuk A, Swallow E. Retrospective US database analysis of persistence with glatiramer acetate vs. available disease-modifying therapies for multiple sclerosis: 2001-2010. BMC Neurol. 2014; 14;14:11.

(5) Lin J, Chow W, Kim MS, Rupnow MF. Real-world treatment pattern and outcomes among patients who took tapentadol IR or oxycodone IR.J Med Econ. 2013; 16(5):685-90.

(6) Oleen-Burkey M, Cyhaniuk A, Swallow E. Treatment patterns in multiple sclerosis: administrative claims analysis over 10 years. J Med Econ. 2013; 16(3):397-406.

(7) Revision 3 of the ENCePP Code of Conduct, available at: http://www.encepp.eu/code_of_conduct/.

# 13. ANNEX 1

### ICD-9 disease classification:

| VARIABLE | CATEGORY | ICD-9 CODES | | | | |
|---|---|---|---|---|---|---|
| Asthma & COPD diagnosis | Asthma | 49300 | 49311 | 49390 | 49310 | 49392 |
| | | 49301 | 49312 | 49391 | 49381 | 49382 |
| | | 49302 | 49310 | | | |
| | Asthma + COPD | 49320 | 49321 | 49322 | | |
| | COPD | 490 | 49122 | 4940 | 49120 | 4928 |
| | | 4910 | 4918 | 4941 | 49121 | 5181 |
| | | 4911 | 4919 | 496 | 4920 | 5182 |
| Other lower respiratory diseases | Chronic | 01000 | 01191 | 01381 | 01611 | 01751 |
| | | 01001 | 01192 | 01382 | 01612 | 01752 |
| | | 01002 | 01193 | 01383 | 01613 | 01753 |
| | | 01003 | 01194 | 01384 | 01614 | 01754 |
| | | 01004 | 01195 | 01385 | 01615 | 01755 |
| | | 01005 | 01196 | 01386 | 01616 | 01756 |
| | | 01006 | 01200 | 01390 | 01620 | 01760 |
| | | 01010 | 01201 | 01391 | 01621 | 01761 |
| | | 01011 | 01202 | 01392 | 01622 | 01762 |
| | | 01012 | 01203 | 01393 | 01623 | 01763 |
| | | 01013 | 01204 | 01394 | 01624 | 01764 |
| | | 01014 | 01205 | 01395 | 01625 | 01765 |
| | | 01015 | 01206 | 01396 | 01626 | 01766 |
| | | 01016 | 01210 | 01400 | 01630 | 01770 |
| | | 01080 | 01211 | 01401 | 01631 | 01771 |
| | | 01081 | 01212 | 01402 | 01632 | 01772 |
| | | 01082 | 01213 | 01403 | 01633 | 01773 |
| | | 01083 | 01214 | 01404 | 01634 | 01774 |
| | | 01084 | 01215 | 01405 | 01635 | 01775 |
| | | 01085 | 01216 | 01406 | 01636 | 01776 |
| | | 01086 | 01220 | 01480 | 01640 | 01780 |
| | | 01090 | 01221 | 01481 | 01641 | 01781 |
| | | 01091 | 01222 | 01482 | 01642 | 01782 |
| | | 01092 | 01223 | 01483 | 01643 | 01783 |
| | | 01093 | 01224 | 01484 | 01644 | 01784 |
| | | 01094 | 01225 | 01485 | 01645 | 01785 |
| | | 01095 | 01226 | 01486 | 01646 | 01786 |
| | | 01096 | 01230 | 01500 | 01650 | 01790 |
| | | 01100 | 01231 | 01501 | 01651 | 01791 |
| | | 01101 | 01232 | 01502 | 01652 | 01792 |
| | | 01102 | 01233 | 01503 | 01653 | 01793 |
| | | 01103 | 01234 | 01504 | 01654 | 01794 |
| | | 01104 | 01235 | 01505 | 01655 | 01795 |
| | | 01105 | 01236 | 01506 | 01656 | 01796 |
| | | 01106 | 01280 | 01510 | 01660 | 01800 |
| | | 01110 | 01281 | 01511 | 01661 | 01801 |
| | | 01111 | 01282 | 01512 | 01662 | 01802 |
| | | 01112 | 01283 | 01513 | 01663 | 01803 |
| | | 01113 | 01284 | 01514 | 01664 | 01804 |
| | | 01114 | 01285 | 01515 | 01665 | 01805 |
| | | 01115 | 01286 | 01516 | 01666 | 01806 |
| | | 01116 | 01300 | 01520 | 01670 | 01880 |

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|---|---|---|---|---|---|---|
| | | 01120 | 01301 | 01521 | 01671 | 01881 |
| | | 01121 | 01302 | 01522 | 01672 | 01882 |
| | | 01122 | 01303 | 01523 | 01673 | 01883 |
| | | 01123 | 01304 | 01524 | 01674 | 01884 |
| | | 01124 | 01305 | 01525 | 01675 | 01885 |
| | | 01125 | 01306 | 01526 | 01676 | 01886 |
| | | 01126 | 01310 | 01550 | 01690 | 01890 |
| | | 01130 | 01311 | 01551 | 01691 | 01891 |
| | | 01131 | 01312 | 01552 | 01692 | 01892 |
| | | 01132 | 01313 | 01553 | 01693 | 01893 |
| | | 01133 | 01314 | 01554 | 01694 | 01894 |
| | | 01134 | 01315 | 01555 | 01695 | 01895 |
| | | 01135 | 01316 | 01556 | 01696 | 01896 |
| | | 01136 | 01320 | 01560 | 01700 | 5110 |
| | | 01140 | 01321 | 01561 | 01701 | 5111 |
| | | 01141 | 01322 | 01562 | 01702 | 4950 |
| | | 01142 | 01323 | 01563 | 01703 | 4951 |
| | | 01143 | 01324 | 01564 | 01704 | 4952 |
| | | 01144 | 01325 | 01565 | 01705 | 4953 |
| | | 01145 | 01326 | 01566 | 01706 | 4954 |
| | | 01146 | 01330 | 01570 | 01710 | 4955 |
| | | 01150 | 01331 | 01571 | 01711 | 4956 |
| | | 01151 | 01332 | 01572 | 01712 | 4957 |
| | | 01152 | 01333 | 01573 | 01713 | 4958 |
| | | 01153 | 01334 | 01574 | 01714 | 4959 |
| | | 01154 | 01335 | 01575 | 01715 | 4760 |
| | | 01155 | 01336 | 01576 | 01716 | 4761 |
| | | 01156 | 01340 | 01580 | 01720 | 500 |
| | | 01160 | 01341 | 01581 | 01721 | 501 |
| | | 01161 | 01342 | 01582 | 01722 | 502 |
| | | 01162 | 01343 | 01583 | 01723 | 503 |
| | | 01163 | 01344 | 01584 | 01724 | 504 |
| | | 01164 | 01345 | 01585 | 01725 | 505 |
| | | 01165 | 01346 | 01586 | 01726 | 5061 |
| | | 01166 | 01350 | 01590 | 01730 | 5062 |
| | | 01170 | 01351 | 01591 | 01731 | 5063 |
| | | 01171 | 01352 | 01592 | 01732 | 5064 |
| | | 01172 | 01353 | 01593 | 01733 | 5069 |
| | | 01173 | 01354 | 01594 | 01734 | 5070 |
| | | 01174 | 01355 | 01595 | 01735 | 5071 |
| | | 01175 | 01356 | 01596 | 01736 | 5078 |
| | | 01176 | 01360 | 01600 | 01740 | 5080 |
| | | 01180 | 01361 | 01601 | 01741 | 5081 |
| | | 01181 | 01362 | 01602 | 01742 | 5082 |
| | | 01182 | 01363 | 01603 | 01743 | 5088 |
| | | 01183 | 01364 | 01604 | 01744 | 5089 |
| | | 01184 | 01365 | 01605 | 01745 | 515 |
| | | 01185 | 01366 | 01606 | 01746 | 51282 |
| | | 01186 | 01380 | 01610 | 01750 | 51283 |
| | | 01190 | 5172 | 5178 | 51883 | 51884 |
| | Non-chronic | 5100 | 51633 | 5185 | 5160 | 5193 |
| | | 5109 | 51634 | 51851 | 5161 | 5194 |
| | | 5130 | 51635 | 51852 | 5162 | 5198 |
| | | 5131 | 51636 | 51853 | 5163 | 51902 |
| | | 5120 | 51637 | 5186 | 51630 | 51909 |

| | | | | | | |
|---|---|---|---|---|---|---|
| | | 5121 | 5164 | 5187 | 51631 | 51911 |
| | | 5122 | 5165 | 51881 | 51632 | 51919 |
| | | 5128 | 51661 | 51882 | 5199 | 5171 |
| | | 51281 | 51662 | 51889 | 51669 | 5180 |
| | | 51284 | 51663 | 51900 | 5168 | 5183 |
| | | 51289 | 51664 | 51901 | 5169 | 5184 |
| Lower respiratory tract infections (LRTIs) | pneumonia | 0330 | 4821 | 48284 | 4803 | 48242 |
| | | 0331 | 4822 | 48289 | 4808 | 48249 |
| | | 0338 | 48230 | 4829 | 4809 | 48281 |
| | | 0339 | 48231 | 4830 | 481 | 48282 |
| | | 0415 | 48232 | 4831 | 4820 | 48283 |
| | | 4800 | 48239 | 4838 | 486 | 4847 |
| | | 4801 | 48240 | 4841 | 4845 | 4848 |
| | | 4802 | 48241 | 4843 | 4846 | 485 |
| | Influenza | 4870 | 48801 | 48812 | 488 | 4881 |
| | | 4871 | 48802 | 48819 | 4880 | 48811 |
| | | 4878 | 48809 | 48881 | 48882 | 48889 |
| | Bronchitis &Bronchiolitis | 4660 | 46611 | 46619 | 5060 | |
| | Other LRTIs | 1363 | 5119 | 78609 | 46421 | 78604 |
| | | 3061 | 78600 | 7862 | 5118 | 78605 |
| | | 46400 | 78601 | 7863 | 51181 | 78606 |
| | | 46401 | 78602 | 78630 | 51189 | 78607 |
| | | 46420 | 78603 | 78631 | 79539 | 78639 |
| | | 7864 | 7867 | 7869 | | |

# 14. ANNEX 2

### Procedure codes for respiratory investigation

| PROCEDURE | CODE | TYPE OF CODE |
|---|---|---|
| CHEST X-RAY | 71010 | CPT-4 |
| CHEST X-RAY | 71015 | CPT-4 |
| CHEST X-RAY | 71020 | CPT-4 |
| CHEST X-RAY | 71021 | CPT-4 |
| CHEST X-RAY | 71022 | CPT-4 |
| CHEST X-RAY AND FLUOROSCOPY | 71023 | CPT-4 |
| CHEST X-RAY | 71030 | CPT-4 |
| CHEST X-RAY AND FLUOROSCOPY | 71034 | CPT-4 |
| CHEST X-RAY | 71035 | CPT-4 |
| CONTRAST X-RAY OF BRONCHI | 71040 | CPT-4 |
| CONTRAST X-RAY OF BRONCHI | 71060 | CPT-4 |
| X-RAY EXAM OF RIBS/CHEST | 71101 | CPT-4 |
| X-RAY EXAM OF RIBS/CHEST | 71111 | CPT-4 |
| MRI CHEST W/O DYE | 71550 | CPT-4 |
| MRI CHEST W/DYE | 71551 | CPT-4 |
| MRI CHEST W/O & W/DYE | 71552 | CPT-4 |
| MRI ANGIO CHEST W OR W/O DYE | 71555 | CPT-4 |
| PLAIN RADIOGRAPHY / THORACIC AORTA | B300 | ICD10 |
| PLAIN RADIOGRAPHY OF THORACIC AORTA | B300ZZZ | ICD10 |
| PLAIN RADIOGRAPHY RESPIRATORY SYS | BB0 | ICD10 |
| PLAIN RADIOGRAPHY / UPPER AIRWAYS | BB0D | ICD10 |
| PLAIN RADIOGRAPHY OF UPPER AIRWAYS | BB0DZZZ | ICD10 |
| PLAIN RADIOGRAPHY / THORACIC DISCS | BR02 | ICD10 |
| PLAIN RADIOGRAPHY OF THORACIC DISCS | BR02ZZZ | ICD10 |
| PLAIN RADIOGRAPHY / THORACIC SPINE | BR07 | ICD10 |
| PLAIN RADIOGRAPHY OF THORACIC SPINE | BR07ZZZ | ICD10 |
| PLAIN RADIOGRAPHY / CHEST | BW03 | ICD10 |
| PLAIN RADIOGRAPHY OF CHEST | BW03ZZZ | ICD10 |
| CT THORAX W/O DYE | 71250 | CPT-4 |
| CT THORAX W/DYE | 71260 | CPT-4 |
| CT THORAX W/O & W/DYE | 71270 | CPT-4 |
| CT ANGIOGRAPHY, CHEST | 71275 | CPT-4 |
| CT CHEST SPINE W/O DYE | 72128 | CPT-4 |
| CT CHEST SPINE W/DYE | 72129 | CPT-4 |
| CT CHEST SPINE W/O & W/DYE | 72130 | CPT-4 |
| CT CT SCAN/THORACIC AORTA | B320 | ICD10 |
| CT SCAN THOR AORTA HI OSMLR CONTRST | B3200ZZ | ICD10 |
| CT CT SCAN THOR AORTA OTH CONTRST | B320YZZ | ICD10 |
| CT SCAN THORACIC AORTA IV OPT COH | B320Z2Z | ICD10 |
| CT CT SCAN OF THORACIC AORTA | B320ZZZ | ICD10 |

| | | |
|---|---|---|
| CT CT SCAN/TRACHEA/AIRWAYS | BB2F | ICD10 |
| CT TR/AIRWAYS HI OSM CONT UN/ENHNCD | BB2F00Z | ICD10 |
| CT SCAN TR/AIRWAYS HI OSMLR CONTRST | BB2F0ZZ | ICD10 |
| CT TR/AIRWAYS L OSM CONT UN/ENHNCD | BB2F10Z | ICD10 |
| CT SCAN TR/AIRWAYS L OSMLR CONTRST | BB2F1ZZ | ICD10 |
| CT TRACH/AIRWAYS OTH CONT UN/ENHNCD | BB2FY0Z | ICD10 |
| CT CT SCAN TR/AIRWAYS OTH CONTRST | BB2FYZZ | ICD10 |
| CT CT SCAN OF TRACHEA/AIRWAYS | BB2FZZZ | ICD10 |
| CT CT SCAN/THORAX | BP2W | ICD10 |
| CT CT SCAN THOR HI OSMOLAR CONTRST | BP2W0ZZ | ICD10 |
| CT CT SCAN THOR LOW OSMOLAR CONTRST | BP2W1ZZ | ICD10 |
| CT CT SCAN THORAX OTHER CONTRAST | BP2WYZZ | ICD10 |
| CT CT SCAN/THORACIC SPINE | BR27 | ICD10 |
| CT CT SCAN OF THORACIC SPINE | BR27ZZZ | ICD10 |
| CT CT SCAN/CHEST & ABDOMEN | BW24 | ICD10 |
| CT CT SCAN CHEST ABD OTH CONTRST | BW24YZZ | ICD10 |
| CT CT SCAN OF CHEST & ABDOMEN | BW24ZZZ | ICD10 |
| CT CT SCAN/CHEST ABDOMEN & PELVIS | BW25 | ICD10 |
| CT CT SCAN CHEST ABDOMEN & PELVIS | BW25ZZZ | ICD10 |
| OTHER X-RAY OF THORAX | 874 | ICD-9 |
| CAT OF THORAX | 8741 | ICD-9 |
| ROUTINE CHEST X-RAY SO DESCRIBED | 8744 | ICD-9 |
| OTHER CHEST X-RAY | 8749 | ICD-9 |
| SOFT TISSUE X-RAY OF THORAX | 873 | ICD-9 |
| ENDOTRACHEAL BRONCHOGRAM | 8731 | ICD-9 |
| OTHER CONTRAST BRONCHOGRAM | 8732 | ICD-9 |
| MEDIASTINAL PNEUMOGRAM | 8733 | ICD-9 |
| SINOGRAM OF CHEST WALL | 8738 | ICD-9 |
| OTHER SOFT TISSUE X-RAY CHEST WALL | 8739 | ICD-9 |
| DIAGNOSTIC PROCEDURES LUNG&BRONCHUS | 332 | ICD-9 |
| THORACOSCOPIC LUNG BIOPSY | 3320 | ICD-9 |
| BRONCHOSCOPY THRU ARTIFICIAL STOMA | 3321 | ICD-9 |
| FIBER-OPTIC BRONCHOSCOPY | 3322 | ICD-9 |
| OTHER BRONCHOSCOPY | 3323 | ICD-9 |
| CLOSED BIOPSY OF BRONCHUS | 3324 | ICD-9 |
| OPEN BIOPSY OF BRONCHUS | 3325 | ICD-9 |
| CLOSED BIOPSY OF LUNG | 3326 | ICD-9 |
| CLOSED ENDOSCOPIC BIOPSY OF LUNG | 3327 | ICD-9 |
| OPEN BIOPSY OF LUNG | 3328 | ICD-9 |
| OTHER DIAGNOSTIC PROC LUNG/BRONCHUS | 3329 | ICD-9 |