



Long Acting Bronchodilators in COPD. Drug Selection by Means of the SOJA Method

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Part 1

Abstract

Objectives: The large number of available medicines in the treatment of COPD makes it almost impossible to have sufficient knowledge of each individual medicine and device, especially for general practitioners. This may lead to suboptimal treatment, more exacerbations, hospitalisations and higher treatment costs. Reducing the number of medicines and devices, based on rational criteria, allows physicians and pharmacists to build experience with a more limited set of medicines and to standardise the inhalation instructions.

Methods: In this study inhaled bronchodilators are compared by means of the SOJA method.

The following selection criteria were applied: approved indications, drug interactions, clinical efficacy, safety, tolerability, dosage frequency and documentation..

Results: Only very limited differences in scores were found between the medicines within classes (LAMA, LABA, LABA/LAMA, LABA/ICS and triple combinations). The highest and lowest scores were within a 5% margin.

Acquisition cost was not taken into account, because this varies with time. In practice acquisition cost is of course an important selection criterion, especially because there are very limited differences between the medicines from a clinical perspective. Exclusion of this criterion also makes this comparison more internationally applicable.

Conclusion: The scores for the individual medicines within each class of inhaled medicines were quite similar. This makes it logical to base formulary decisions on the properties of the devices (and acquisition cost). This analysis will be published in a separate article. .

Keywords: Long Acting Beta Sympathomimetics [LABA]; Long Acting Muscarine Antagonists [LAMA]. Inhaled corticosteroids (ICS).

Introduction

Effective bronchodilatation is the cornerstone of pharmacological treatment of COPD. Several different treatment options are

available, such as long acting beta sympathomimetics [LABA], long acting muscarine antagonists [LAMA], combinations of both, combinations of LABA and inhaled corticosteroids [ICs] and triple

combinations of LABA, LAMA and ICS. Each treatment option is used in different stages of COPD. Besides these pharmacological options, different inhalation forms, such as Metered dose inhalers [MDIs], Dry powder inhalers [DPIs] and soft mist inhalers are available.

The large number of available medicines and devices makes it almost impossible to have sufficient knowledge of each individual medicine and devices, especially for general practitioners. This may lead to suboptimal treatment, more exacerbations, hospitalisations and higher treatment costs.

Reducing the number of medicines and devices, based on rational criteria, allows physicians and pharmacists to build experience with a more limited set of medicines and to standardise the inhalation instructions.

This makes it relevant to make a rational selection of treatment options, so that individual patients are treated with bronchodilators and devices in such a way that treatment is optimised.

Research question

The authors of the present article were members of the Expert Group [Working Party] of the Dutch Long Association. The aim of this Working Party [consisting of pulmonologists, general practitioners, researchers and hospital- and community pharmacists] was to develop an online program based on criteria for the selection of inhaled medication for the maintenance treatment of COPD in the Netherlands.

In this study long acting inhaled bronchodilators [monotherapy in combination with other bronchodilators or inhaled corticosteroids] are compared by means of the SOJA method. The System of Objectified Judgement Analysis [SOJA] method is a model for rational drug selection.

Methods

Inclusion and exclusion criteria

This analysis was performed to compare soft mist inhalers and Dry powder inhalers [DPIs]. Metered dose inhalers [MDIs] were excluded from the analysis, with the exception of Trimbrow [for reasons of comparison within the Triple combinations], because patient populations treated with MDIs may be different from DPIs.

Applied methodology

The relevant selection criteria for a certain group of drugs are defined and judged by a panel of experts and each selection criterion is given a relative weight. The more important that a selection

criterion is considered, the higher the relative weight that is given to that criterion. The ideal properties for each selection criterion are determined and each drug is scored as a percentage of the score of the ideal drug for all selection criteria. The drugs with the highest total score are most suitable for formulary inclusion [1].

An interactive program will be made available, in which users of the method can assign their own weighting to each selection criterion, thereby making their own ranking of the medicines.

The following selection criteria were applied:

Selection criteria

| Criterion | Relative weight |
|-------------------------------------|-----------------|
| Indications | 50 |
| Interactions | 50 |
| Efficacy | 500 |
| Safety | 150 |
| Tolerability | 100 |
| Dosage Frequency | 80 |
| Documentation (clinical studies) | 35 |
| Documentation (clinical experience) | 35 |
| Total score | 1000 |

Table a

The following drugs were included in the analysis

Long acting beta sympathicomimetics [LABA]

- Formoterol [Foradil DPI, Oxis Turbuhaler, Formoterol Sandoz Novolizer, Formoterol Easyhaler]
- Indacaterol [Onbrez Breezhaler]
- Olodaterol [Striverdi Respimat]
- Salmeterol [Serevent Diskus/Accuhaler]

Long acting muscarine antagonists [LAMA]

- Acclidinium [Eklira Genuair]
- Glycopyrronium [Seebri Breezhaler]
- Tiotropium [Spiriva inhalation powder and Respimat]
- Tiotropium [Tiotrus Zonda inhalation powder]
- Umeclidinium [Incruse Ellipta]

Combinations of two bronchodilators [LABA/LAMA]:

- Acclidinium/formoterol [Duaklir Genuair]

- Glycopyrronium/indacaterol [Ultibro Breezhaler]
- Olodaterol/tiotropium [Spiolto Respimat]
- Umeclidinium/vilanterol [Anoro Ellipta]

Combinations of bronchodilators and inhaled corticosteroids [LABA/ICS]:

- Formoterol/beclomethasone Nexthaler [Foster]
- Formoterol/budesonide DPI [Symbicort Turbuhaler; Duoresp Spiromax, Bufoleer Easyhaler]
- Salmeterol/fluticasone propionate DPI [Seretide, Generic: SF Elpenhaler, Airflusal Forspiro DPI]
- Vilanterol/fluticasone furoate [Relvar Ellipta].

Triple combinations [two bronchodilators and an inhaled corticosteroid] [LABA/LAMA/ICS]:

- Fluticasone furoate/umeclidinium/vilanterol DPI [Trelegy Ellipta]
- Beclomethasone/formoterol/glycopyrronium MDI [Trimbow].

The combination formoterol/fluticasone propionate [Flutiform] was not included in the manuscript, because this combination is only approved in asthma.

After the authors had determined the set of selection criteria, Medline, Embase and the Cochrane database were searched and references from review articles obtained.

Selection criteria

The following selection criteria were applied.

Number of approved indications

This was judged as follows [data derived from the Summaries of Product Characteristics [SPC].

From a formulary perspective, it is an advantage that a medicine is approved for both COPD and asthma.

When a medicine is approved for COPD alone, it scores 70%. When it is approved for asthma as well, it is awarded 100%.

Drug interactions

This criterion is only of importance in formulary decision making as the vast majority of patients treated with long acting bronchodilators will not experience any drug interactions. Drug inter-

actions may result in a reduction of clinical efficacy of the COPD medicine in question or in a reduction of the clinical efficacy of the other drug, with which the interaction occurs. Interactions may also give rise to increased toxicity of one or both compounds. The more frequent these interactions occur and the more serious the consequences are, the lower the score for the drug in question.

Clinical efficacy

The judgement of the relative clinical efficacy should ideally be based on a large number of direct comparative studies between the combinations using clinically relevant endpoints. Unfortunately, the number of direct comparative studies is quite limited. Double-blind comparative studies with dry powder inhalers have hardly been done, because of the necessity of the companies to participate in such a double-blind, double-dummy study.

The following rules of play were used:

- Only studies in COPD patients
- Only studies in > 25 patients
- Only studies with specific formulations
- Only studies with a duration of at least 2 weeks

Using the following endpoints:

- Effect on lung function
- Effects on frequency of exacerbations
- Use of "rescue medication"
- Effects in decrease in lung function
- Effects on hospitalisation rate
- Effects on quality of life
- Effects on mortality.

Safety

Safety is an important selection criterion for each individual group of medicines, especially for those medicines which are used chronically. Safety [the lack of occurrence of severe adverse reactions] was determined from clinical studies [direct comparisons between 2 or more medicines of from placebo-controlled studies], meta-analyses and database studies.

Tolerability

Tolerability is an important selection criterion for each individual group of medicines, especially for those medicines which

are used chronically. Tolerability [the lack of occurrence of non-severe reactions] was determined from clinical studies [direct comparisons between 2 or more medicines or from placebo-controlled studies], meta-analyses and database studies.

Dosage frequency

The dosage frequency plays an important role in patient compliance. Compliance is not usually a problem in patients taking drugs once or twice daily, but decreases considerably in the event that 3-4 dosages are to be taken daily. The method of evaluation of this criterion corresponded with that of all of the other SOJA scores:

- Once daily: 100%
- One or twice daily: 90%
- Twice daily: 80%
- Three times daily: 40%.

Documentation [clinical studies]

The two sub criteria are indicative of the overall clinical documentation of the drugs in well designed [preferably double-blind] randomised controlled clinical studies. A large number of clinical studies and a large number of patients included in these studies leave no doubt about the clinical efficacy and tolerability of this drug in the studied population:

- The number of comparative studies [50%]
- Five percent of the maximum score was assigned for each study of a specific drug. As a result, the score for 20 studies is 100%.
- The number of patients in these studies [50%]
- For every 10 patients participating in these studies 1% of the maximum score was assigned. As a result, the score for 1000 patients is 100%.

Documentation [clinical experience]

The two sub criteria are indicative of the overall clinical experience with the drug. These sub criteria may introduce a bias to the advantage of older drugs, but this is done intentionally. The safety of a newly introduced drug cannot be guaranteed from the results of clinical studies, in which only a relatively small number of patients were included and most patients at risk for the development of adverse reactions [eg patients with diminished renal function] were excluded. Both the number of patients that has been treated

on a worldwide bases and the period that a certain drug has been available are of importance, as it may take time until adverse reactions occur:

- The number of years on the market [50%].
- Every year a certain drug has been on the market represents 10% of the score. If a drug has been on the market for at least 10 years, the score is 100%.
- Number of patient days worldwide [50%].
- Every one million of patient days of experience represents 1% of the score. If the number of patients days of experience exceeds 100 million, the score is 100%.

Results

Number of approved indications

Indacaterol, olodaterol [and combination], aclidinium [and combination], glycopyrronium [and combination], umeclidinium [and combination] and the triple combinations are only approved for the treatment of COPD and are awarded 70%.

The other medicines/combinations are approved for both COPD and asthma and score 100%.

Drug interactions

Unless otherwise stated, all data were derived from the Summaries of Product Characteristics of the various products.

Valid for all sympathomimetic agents

Concomitant administration of other sympathomimetic medicinal products [alone or as part of combination therapy] may potentiate adverse reactions.

Inhaled sympathomimetic products should not be used in conjunction with other long-acting beta2-adrenergic agonists or medicinal products containing long-acting beta2-adrenergic agonists.

Beta-adrenergic blockers

Beta-adrenergic blockers and beta 2-adrenergic agonists may weaken or antagonise the effect of each other when administered concurrently. Therefore indacaterol should not be given together with beta adrenergic blockers [including eye drops] unless there are compelling reasons for their use. Where required, cardioselective

tive beta-adrenergic blockers should be preferred, although they should be administered with caution.

Hypokalaemic treatment

Concomitant hypokalaemic treatment with methylxanthine derivatives, steroids, or non-potassium sparing diuretics may potentiate the possible hypokalaemic effect of beta2-adrenergic agonists, therefore caution is required.

Valid for all anticholinergic agents

Co-administration of acclidinium bromide with other anticholinergic-containing medicinal products has not been studied and is not recommended.

Acclidinium

Although no formal *in vivo* drug interaction studies have been performed, inhaled acclidinium bromide has been used concomitantly with other COPD medicinal products including sympathomimetic bronchodilators, methylxanthines, and oral and inhaled steroids without clinical evidence of drug interactions.

In vitro studies have shown that acclidinium bromide or the metabolites of acclidinium bromide at the therapeutic dose are not expected to cause interactions with P-glycoprotein [P-gp] substrate drugs or drugs metabolised by cytochrome P450 [CYP450] enzymes and esterases.

Formoterol

No specific drug interactions have been performed with formoterol.

There is a theoretical risk that simultaneous use with other medicines which may affect the QT-interval may give rise to a pharmacodynamic interaction, leading to a risk of ventricular arrhythmias.

Concomitant administration of other sympathomimetic medicinal products [alone or as part of combination therapy] may potentiate adverse reactions to formoterol.

The risk of hypoglycaemia is increased if [i.v. or oral] corticosteroids are given simultaneously with formoterol.

There is an increased risk of arrhythmias in patients undergoing anaesthesia with halogenated hydrocarbons.

Formoterol does not inhibit the CYP450 enzymes at therapeutically relevant concentrations.

Concomitant treatment with monoamine oxidase inhibitors including agents with similar properties such as furazolidone and procarbazine may precipitate hypertensive reactions.

Glycopyrronium

In a clinical study in healthy volunteers, cimetidine, an inhibitor of organic cation transport which is thought to contribute to the renal excretion of glycopyrronium, increased total exposure [AUC] to glycopyrronium by 22% and decreased renal clearance by 23%. Based on the magnitude of these changes, no clinically relevant drug interaction is expected when glycopyrronium is co-administered with cimetidine or other inhibitors of organic cation transport.

Concomitant administration of glycopyrronium and orally inhaled indacaterol, a beta2-adrenergic agonist, under steady-state conditions of both active substances did not affect the pharmacokinetics of either medicinal product.

Indacaterol

Metabolic and transporter based interactions

Inhibition of the key contributors of indacaterol clearance, CYP3A4 and P-glycoprotein [P-gp] raises the systemic exposure of indacaterol by up to two-fold. The magnitude of exposure increases due to interactions does not raise any safety concerns given the safety experience of treatment with indacaterol in clinical studies of up to one year at doses up to twice the maximum recommended therapeutic dose.

Indacaterol has not been shown to cause interactions with medicinal products administered concomitantly. *In vitro* investigations have indicated that indacaterol has negligible potential to cause metabolic interactions with medicinal products at the systemic exposure levels achieved in clinical practice.

Olodaterol

There is a theoretical risk that simultaneous use with other medicines which may affect the QT-interval may give rise to a pharmacodynamic interaction, leading to a risk of ventricular arrhythmias.

Concomitant administration of other sympathomimetic medicinal products [alone or as part of combination therapy] may potentiate adverse reactions to olodaterol.

No drug interaction was observed between olodaterol and fluconazole [a strong inhibitor of CYP 2C9].

Simultaneous use with ketoconazole [strong P-gp and CYP inhibitor] increased the systemic exposure of olodaterol by 70%, but dose adjustment is not necessary.

Use of olodaterol and tiotropium in combination did not affect systemic exposure of the medicines.

In vitro studies have showed no effect of olodaterol on CYP isoenzymes or drug transporters.

Salmeterol

Co-administration of ketoconazole [400 mg orally once daily] and salmeterol [50 mcg inhaled twice daily] in 15 healthy subjects for 7 days resulted in a significant increase in plasma salmeterol exposure [1.4-fold C_{max} and 15-fold AUC]. This may lead to an increase in the incidence of other systemic effects of salmeterol treatment [e.g. prolongation of QTc interval and palpitations] compared with salmeterol or ketoconazole treatment alone.

Clinically significant effects were not seen regarding blood pressure, heart rate, blood glucose and blood potassium levels. Co-administration with ketoconazole did not increase the elimination half-life of salmeterol or increase salmeterol accumulation with repeat dosing.

The concomitant administration of ketoconazole should be avoided, unless the benefits outweigh the potentially increased risk of systemic side effects of salmeterol treatment. A similar risk of interaction with other potent CYP3A4 inhibitors [e.g. itraconazole, telithromycin, ritonavir] is likely.

Co-administration of erythromycin [500mg orally three times a day] and salmeterol [50µg inhaled twice daily] in 15 healthy subjects for 6 days resulted in a small but non-statistically significant increase in salmeterol exposure [1.4-fold C_{max} and 1.2-fold AUC]. Co-administration with erythromycin was not associated with any serious adverse effects.

Tiotropium

No formal drug interaction studies have been performed with tiotropium, but in clinical studies the drug was combined without problems with sympathomimetics, methylxanthines and oral and inhaled corticosteroids.

Umeclidinium

Clinically significant interactions mediated by umeclidinium bromide at clinical doses are considered unlikely due to the low plasma concentrations achieved after inhaled dosing.

Metabolic and transporter based interactions

Umeclidinium bromide is a substrate of cytochrome P450 2D6 [CYP2D6]. The steady-state pharmacokinetics of umeclidinium bromide were assessed in healthy volunteers lacking CYP2D6 [poor metabolisers]. No effect on the AUC or C_{max} of umeclidinium was observed at a dose 4-fold higher than the therapeutic dose. An approximately 1.3-fold increase in umeclidinium bromide AUC was observed at an 8-fold higher dose with no effect on the C_{max} of umeclidinium bromide. Based on the magnitude of these changes, no clinically relevant drug interaction is expected when umeclidinium is co-administered with CYP2D6 inhibitors or when administered to subjects genetically deficient in CYP2D6 activity [poor metabolizers].

Formoterol/budesonide

See formoterol for drug interactions of formoterol.

Potent inhibitors of CYP3A4 [e.g., ketoconazole, itraconazole, voriconazole, posaconazole, clarithromycin, telithromycin, nefazodone and HIV protease inhibitors] are likely to markedly increase plasma levels of budesonide and concomitant use should be avoided. If this is not possible the time interval between administration of the inhibitor and budesonide should be as long as possible. In patients using potent CYP3A4 inhibitors, formoterol/budesonide maintenance and reliever therapy is not recommended.

The potent CYP3A4 inhibitor ketoconazole, 200 mg once daily, increased plasma levels of concomitantly orally administered budesonide [single dose of 3 mg] on average six-fold. When ketoconazole was administered 12 hours after budesonide the concentration was on average increased only threefold showing that separation of the administration times can reduce the increase in plasma levels. Limited data about this interaction for high-dose in-

haled budesonide indicates that marked increase in plasma levels [on average four fold] may occur if itraconazole, 200 mg once daily, is administered concomitantly with inhaled budesonide [single dose of 1000 µg]:

- Olodaterol/tiotropium
- See olodaterol for drug interactions of olodaterol
- See tiotropium for drug interactions of tiotropium
- Salmeterol/Fluticasone
- See salmeterol for drug interactions of salmeterol
- See vilanterol/fluticasone for drug interactions of fluticasone
- Umeclidinium/vilanterol
- Metabolic and transporter based interactions.

Vilanterol is a substrate of cytochrome P450 3A4 [CYP3A4]. Concomitant administration of strong CYP3A4 inhibitors [e.g. ketoconazole, clarithromycin, itraconazole, ritonavir, telithromycin] may inhibit the metabolism of, and increase the systemic exposure to, vilanterol. Co-administration with ketoconazole [400 mg] in healthy volunteers increased mean vilanterol AUC[0-t] and Cmax, 65% and 22% respectively. The increase in vilanterol exposure was not associated with an increase in beta-adrenergic agonist related systemic effects on heart rate, blood potassium or QT interval [corrected using the Fridericia method]. Care is advised when co-administering umeclidinium/vilanterol with ketoconazole and other known strong CYP3A4 inhibitors as there is potential for an increased systemic exposure to vilanterol, which could lead to an increase in the potential for adverse reactions. Verapamil, a moderate CYP3A4 inhibitor, did not significantly affect the pharmacokinetics of vilanterol.

Both umeclidinium and vilanterol are substrates of the P-glycoprotein transporter [P-gp]. The effect of the moderate P-gp inhibitor verapamil [240 mg once daily] on the steady-state pharmacokinetics of umeclidinium and vilanterol was assessed in healthy volunteers. No effect of verapamil was observed on umeclidinium or vilanterol Cmax. An approximately 1.4-fold increase in umeclidinium AUC was observed with no effect on vilanterol AUC. Based on the magnitude of these changes, no clinically relevant drug interaction is expected when umeclidinium/vilanterol is co-administered with P-gp inhibitors [2].

Vilanterol/fluticasone

Interaction with CYP3A4 inhibitors

Fluticasone furoate and vilanterol are both rapidly cleared by extensive first pass metabolism mediated by the liver enzyme CYP3A4.

Caution is advised when co-administering with strong CYP3A4 inhibitors [e.g. ketoconazole, ritonavir] as there is potential for increased systemic exposure to both fluticasone furoate and vilanterol, and concomitant use should be avoided.

A drug interaction study was performed in healthy subjects with the combination and the strong CYP3A4 inhibitor ketoconazole [400 mg]. This increased mean fluticasone furoate AUC [0-24] and Cmax by 36% and 33%, respectively. The increase in fluticasone furoate exposure was associated with a 27% reduction in 0-24 hours weighted mean serum cortisol. Co-administration increased mean vilanterol AUC and Cmax by 65% and 22%, respectively [3].

Interaction with P-glycoprotein inhibitors

Fluticasone furoate and vilanterol are both substrates of P-glycoprotein [P-gp]. A clinical pharmacology study in healthy subjects with co-administered vilanterol and the potent P-gp and moderate CYP3A4 inhibitor verapamil did not show any significant effect on the pharmacokinetics of vilanterol. Clinical pharmacology studies with a specific P-gp inhibitor and fluticasone furoate have not been conducted.

Most LABA and LAMA show few clinically relevant drug interactions. Monotherapies are awarded 80%, with the exception of salmeterol and budesonide, which shows drug interactions with inhibitors of CYP450. Salmeterol and budesonide are awarded 70%.

Combinations of LABA and LAMA are awarded 70%.

Combinations of LABA and inhaled corticosteroids are also awarded 70%, with the exception of combinations with salmeterol or budesonide, which may show interactions with inhibitors of CYP450. These formulations score 60%.

Triple combinations are also awarded 70%.

Clinical efficacy

All medicines have been compared to placebo. These studies are not discussed in detail in this manuscript when the scope of

the study was limited to the effects on pulmonary function. The studies were however taken into consideration for the criterion documentation. When effects on clinical endpoints [hospitalisation rate, exacerbations, quality of life and mortality] were investigated in placebo-controlled studies, these are discussed in more detail.

Several studies were excluded because of a short duration of treatment, too small sample size or the use of devices not included in this analysis [4-37].

The most important methodological aspects, patient characteristics, baseline data and results [efficacy, safety and tolerability] are presented as much as possible in the form of tables. Placebo controlled studies without active controls were not included in the tables, but were taken into consideration for judgement of documentation.

The study details regarding the design and results of the studies is provided in a separate document [38-108].

Clinical efficacy

Acclidinium

Placebo-controlled studies

Acclidinium was compared to placebo in several double-blind studies. Acclidinium was consistently more effective concerning FEV1 and other lung function parameters as well as on exercise endurance [109-115]. No significant effect on exacerbation frequency was found in individual studies.

A Cochrane meta-analysis was performed on all available acclidinium studies, which included 12 multicenter RCTs randomly assigning over 9,500 participants with stable COPD. All studies were industry-sponsored. There was no difference between acclidinium and placebo in all-cause mortality and number of patients with exacerbations requiring a short course of oral steroids or antibiotics, or both [moderate quality]. Acclidinium improved quality of life [SGRQ total score] when compared to placebo. Acclidinium also resulted in a significantly greater improvement in pre-dose FEV1 than placebo with a mean difference of 0.09 L. Acclidinium reduced the number of patients with exacerbations requiring hospitalisation [OR 0.64] compared to placebo [116].

Acclidinium vs formoterol

Two studies compared acclidinium and formoterol [as well as combination of both medicines]. Although acclidinium tended to

have slightly more favourable effects on lung function parameters, no significant differences in clinical efficacy were seen between both medicines [40,41]. These studies were not taken into consideration for the documentation of formoterol, because the Genuair device was used. Formoterol is not available as such as monotherapy in the Genuair device.

Acclidinium vs tiotropium

Acclidinium and tiotropium were compared in two studies. No significant differences in clinical efficacy regarding lung function parameters were seen [38,39].

A systematic review and meta-analysis suggested a similar efficacy of acclidinium [400 mcg bid] compared to glycopyrronium and tiotropium [117]. It should however be taken into consideration that no direct comparative studies were performed between acclidinium and glycopyrronium. The results were based on indirect comparisons.

Formoterol

Placebo-controlled studies

A number of studies was performed comparing formoterol Turbuhaler to placebo [118-121] or a comparison with placebo, in combination with ipratropium [122]. All studies showed a significant increase in FEV1 and symptom scores. Similar effects were seen in one study using the Aerolizer [123]. One study was not included in the Tables, because an American device, not available in Europe, was used [124].

Two studies were excluded because it was not clear how many patients with either asthma or COPD were included [125,126].

Formoterol vs tiotropium

One study compared formoterol [Aerolizer] and tiotropium [Handihaler] and their combination in a double-blind, crossover design. All treatments were given for 6 weeks in a study population with mainly patients with severe COPD. Few significant differences were found between both bronchodilators. Only the outcome measure FEV1 and FEV1 response from 0 - 12 hours was significantly better for tiotropium. The combination was more effective than formoterol on all studied endpoints [44].

Formoterol vs AZD3199

One study compared formoterol [Turbuhaler] to AZD3199, an ultra-long acting bronchodilator, with a duration of action of over

24 hours. No significant differences were observed in any efficacy endpoint [45].

Formoterol vs glycopyrronium

Three studies compared formoterol to glycopyrronium, both administered as MDI. The combination of both medicines was also included in these studies. These studies are not included in the tables, because a different inhaler [MDI] was used [127-129].

Formoterol vs olodaterol

Four studies compared formoterol Aerolizer to olodaterol Respimat [and placebo]. The results were reported in two publications. No significant differences in endpoints [FEV1, FEV AUC, SGRQ] between both active treatments were observed [54,55].

Formoterol vs formoterol/budesonide

Formoterol and the combination formoterol and budesonide were compared in several double-blind studies, mostly using the Turbuhaler device for both preparations. In Tables 1-6 only the results for formoterol and the combination [and placebo if applicable] were taken into consideration. The results of monotherapy budesonide were not included, because it was not considered to be relevant for this matrix focusing on long acting bronchodilators [47-51].

The combination was consistently more effective than formoterol in effects on FEV1 and other lung function parameters and on quality of life [HRQL or SGQL], as well as [in studies powered to show effects on exacerbations] on exacerbation frequency, frequency of severe exacerbations, time to first exacerbation [47-51].

Glycopyrronium

Placebo-controlled studies

Studies investigating glycopyrronium consistently showed significantly better effects on FEV1 compared to placebo [130-135]. Some studies also showed significantly better effects on SGRQ, TDI and exercise endurance than placebo [132-134]. One study demonstrated a significant prolongation of the time to first exacerbation [132]. Another study showed superiority versus placebo when added to beclomethasone plus formoterol [136].

One placebo-controlled study investigating the effects of triple therapy [addition of glycopyrronium to budesonide and formoterol] showed better lung function outcomes in the glycopyrronium arm [137].

Glycopyrronium vs tiotropium

Three studies compared formoterol [Aerolizer] and tiotropium [Handihaler] in a double-blind or open label design. In one study, both medicines were added to the combination salmeterol/fluticasone. Glycopyrronium and tiotropium showed similar effects on FEV1, SGRQ and use of rescue medication, with no relevant differences between the drugs [56]. Another study investigated monotherapy with glycopyrronium, tiotropium and placebo. Clinical efficacy of both medicines was comparable and superior to placebo [57]. Another study showed similar efficacy on lung function parameters of both compounds, with significantly better effects in lung function parameters at day 1 for glycopyrronium. Results after 12 weeks were similar for both drugs [58].

Indacaterol

Placebo-controlled studies

Several placebo-controlled trials showed better efficacy regarding FEV1 and SGRQ scores [138-140]. One study showed a lower incidence of exacerbations compared to placebo [140].

A Cochrane meta-analysis on all available studies, which included multicentre randomised controlled trials randomly assigning over 9,600 participants with stable COPD was published in 2015 [141]. Placebo-controlled trials were identified as well as trials in which indacaterol was compared to other beta2-agonists. The primary objectives were to compare trough FEV1 at the end of dosing, exacerbation rates and quality of life. Compared with placebo, a significant improvement of 149 ml in trough FEV1 was seen with indacaterol. A significant improvement in SGRQ score [3.60 points decrease] as well as in the proportion of participants experiencing a clinically relevant improvement in SGRQ score: OR 1.63 [141].

A post-hoc analysis of 6 months data from 3 large placebo controlled studies showed a lower incidence of exacerbations [RR 0.69 for 150 mg and 0.71 for 300 mg, respectively] [142].

Active controls

Indacaterol was compared to tiotropium in three studies, with salmeterol in two and with salmeterol/fluticasone in one study. Indacaterol was at least as effective as tiotropium in effects on lung function, SGRQ and TDI [59-61], but there was uncertainty concerning its effects on exacerbation, non-inferiority could not be demonstrated [61].

Indacaterol was more effective than salmeterol on lung function parameters, TDI and use of rescue medication [Ind 18, Ind 19]. In a study investigating current users of salmeterol/fluticasone, free of exacerbations in the year previous to the study, a double-blind switch to salmeterol was as effective as maintaining patients on the combination [64].

The same meta-analysis as stated earlier studied indacaterol vs twice daily beta2-agonists. Compared formoterol and salmeterol, a small but statistically significant increase in FEV1 was seen with indacaterol. The effects on mean SGRQ scores and the proportions of participants achieving clinically relevant improvements in SGRQ scores were not statistically significant different between indacaterol and active comparators. Data were lacking power to allow a reliable analysis of exacerbation rates [141].

Another meta-analysis was performed comparing indacaterol with tiotropium. FEV1 was measured at weeks 12 and 26 and SGRQ total scores were not significantly different [143].

A meta-analysis performed by the manufacturer of indacaterol concluded that the efficacy of indacaterol was comparable to formoterol/budesonide and salmeterol/fluticasone [144].

The timing of administration of indacaterol does not affect clinical efficacy [145].

Olodaterol

Placebo-controlled studies

One placebo-controlled trial showed better efficacy regarding FEV1 and rescue medication use [146]. Another placebo-controlled study showed positive effects on exercise endurance [147].

Olodaterol versus tiotropium

Two studies compared olodaterol to tiotropium [and placebo]. The results were reported in one publication. No differences in clinical efficacy were observed between both bronchodilators [74].

Salmeterol

Placebo-controlled studies

Five placebo-controlled trials showed better efficacy in lung function parameters and SGRQ [148-152]. Only one study showed a positive effects on exacerbations [S9]. The Torch study also showed a positive effect on moderate to severe exacerbations compared to placebo [81].

These results were confirmed in a meta-analysis [153].

Salmeterol versus tiotropium

Salmeterol MDI was compared to tiotropium Handihaler in 4 double-blind, double-dummy studies. Tiotropium was consistently more effective regarding lung function test, TDI and SGRQ [77,78,80].

The large scale POET study investigated both medicines regarding effects on exacerbations. Tiotropium had significantly more favourable effects on: the time to first exacerbation [187 vs 145 days: risk reduction 17%], the time to first severe exacerbation [hazard ratio 0.72], the annual number of moderate to severe exacerbations [0.64 vs 0.72, rate ratio 0.89] and the annual number of severe exacerbations [0.09 vs 0.13, rate ratio 0.73] [79,154]. The incidence of exacerbations was also significantly lower for tiotropium in patients with moderate COPD [155]. Another smaller scale study also showed positive effects of tiotropium concerning exacerbations [80].

Salmeterol versus theophylline

Salmeterol was more effective than theophylline measured by pulmonary function tests in one study [156] and the combination of both agents was more effective than monotherapy in another study [157].

Tiotropium

Placebo controlled studies

Tiotropium was more effective than placebo regarding lung function tests, exercise endurance, quality of life and exacerbation rate [158-173].

The large scale Uplift study showed improvements in lung function, quality of life and exacerbation rate during a 4-year study period, but did not affect the rate of decline in FEV1 [174]. A pre-specified subgroup analysis of patients with stage II COPD showed a lower rate of decline of FEV1 [43 vs 49 ml per year] [175]. Mortality was reduced by tiotropium vs placebo; HR 0.84, 95% CI 0.73-0.97 [176].

Tiotropium versus ipratropium

Comparative studies between tiotropium and ipratropium were not included in Tables 1-6, because these studies fall outside the scope of this analysis. These studies were taken into consideration for the criterion documentation.

A Cochrane meta-analysis was performed [in 2013] comparing tiotropium to ipratropium. The authors showed that tiotropium improved lung function, resulted in fewer hospital admissions [including those for exacerbations of COPD], fewer exacerbations of COPD and improved quality of life compared with ipratropium bromide [177].

Tiotropium versus long acting beta-agonists

A Cochrane meta-analysis has been performed [in 2013] comparing tiotropium to long acting beta-agonists [LABA] in the maintenance treatment of COPD. Seven clinical studies [12,223 patients with COPD in total] were included in the review. Tiotropium [delivered by HandiHaler in all studies] was compared with salmeterol [four studies including 8,936 participants], formoterol [one study, 431 patients] or indacaterol [two studies, 2,856 patients].

Due to a high level of heterogeneity amongst studies data could not be pooled regarding quality of life scores.

There was no statistically significant difference in the effect on FEV1 or symptom score between tiotropium and LABA.

Tiotropium reduced the number of patients experiencing exacerbations compared with LABA [odds ratio [OR] 0.86. It is estimated that one additional person on tiotropium will stay exacerbation-free for every 29 people treated with tiotropium instead of LABA for a year.

Tiotropium was associated with a reduction in number of COPD exacerbations leading to hospitalisation compared with LABA treatment [OR 0.87], but not in the overall rate of all-cause hospitalisations.

No statistically significant difference in mortality was observed between the treatment groups [178].

One study compared salmeterol/fluticasone and tiotropium in 1323 patients during 2 in a double-blind, double dummy design. The modeled yearly exacerbation frequency was almost identical in the groups: 1.28 in the combination group versus 1.32 in the tiotropium group [179].

Tiotropium plus combinations of long acting bronchodilators and inhaled corticosteroids

A Cochrane meta-analysis [published in 2013] investigated the addition of tiotropium to combinations of bronchodilators and corticosteroids [or vice versa]. The authors concluded that the benefits

of the combination has not been demonstrated regarding effects on mortality, hospitalisation and exacerbations of COPD. The addition of combination treatment to tiotropium has shown improvements in average health-related quality of life and lung function [180]. Studies investigating the added value of combining treatments were not included in this analyses, except when the effects of tiotropium and combination treatment as separate arms were also studied. For this reason studies [181-186] were excluded.

Tiotropium was superior to salmeterol when added to fluticasone [187].

Tiotropium was more effective than ipratropium [188-190] and improved symptoms when added to theophylline [191].

Tiotropium doses of 5 and 10 mcg delivered by Respimat was as effective as 18 mcg delivered by Handihaler [192].

Umeclidinium

Placebo-controlled studies

Addition of umeclidinium to fluticasone/vilanterol resulted in significantly better clinical efficacy than placebo regarding FEV1 and SGRQ [193]. The same results were obtained in another study comparing umeclidinium or placebo added to inhaled corticosteroid/long acting beta 2 agonist [194].

Comparison with salmeterol/fluticasone

Umeclidinium Ellipta [62.5 microg] was more effective than tiotropium Handihaler regarding effects on FEV1 at day 85 in a direct comparative study [89].

Vilanterol

Placebo-controlled studies

Vilanterol was more effective than placebo in improving lung function in one study [195].

Aclidinium/Formoterol

Placebo-controlled studies

Aclidinium/formoterol was more effective than placebo in improving lung function in one study [196].

Comparison with individual components

The combination acclidinium/formoterol [400/6 mcg and 400/12 mcg] was compared to the individual components in three double blind studies [A10, A11, A11w]. The main results are sum-

marised in table 1-6. The AUGENT COPD study showed a significant difference between the combinations and the individual components on improvement of 1-hour post dose FEV1 and between the 400/12 mcg combination and formoterol on the trough FEV1. The combinations were also more effective on improvement of TDI than the components on some, but not all time points [A10]. Similar results were obtained in the ACLIFORM-COPD study [41].

A combined analysis of both above studies demonstrated a significant difference between the 400/12 mcg combination and the individual components regarding effects on TDI focal score at week 24, improvements in E-RS total score, overall night-time and early morning symptom severity and limitation of early-morning activities. No significant difference was observed between the combinations and their components on the frequency of moderate to severe exacerbations [using the HealthCare Resource Utilisation, HRCU, definition], but a significant reduction was seen compared to placebo. When the EXACT [EXAcerbations of Chronic pulmonary disease Tool respiratory symptoms questionnaire] definition of an exacerbation was used, the rate of exacerbations was significantly lower for the 400/12 mcg combination compared to acclidinium and placebo. The time to first exacerbation [any of the two definitions] was significantly prolonged for the 400/12 mcg combination compared to placebo, but not to acclidinium or formoterol [198].

Comparison with salmeterol/fluticasone

The combination acclidinium/formoterol [400/12 mcg] was compared to salmeterol/fluticasone [50/500 mcg bid] in patients with stable moderate to severe COPD in the AFFIRM COPD study. The primary endpoint was FEV1 at week 24. The main results are summarised in table 1-6. Both combinations showed similar effects on symptom control and exacerbation frequency. The former combination had stronger effects on FEV1 [42].

Formoterol/beclomethasone

Formoterol/beclomethasone and formoterol/budesonide showed similar efficacy in a direct comparative study [51]. Another study compared formoterol/beclomethasone to salmeterol/fluticasone, showing significantly better efficacy on FEV1, but similar effects on all other efficacy parameters [52].

Formoterol/budesonide

Formoterol/budesonide vs placebo

One study compared the combination to placebo, both added to tiotropium. The combination was superior to placebo on all inves-

tigated endpoints [199].

Formoterol/budesonide vs formoterol

See section on formoterol

A Cochrane meta-analysis [published in 2013] investigated the relative efficacy of LABA plus inhaled corticosteroid combinations compared to LABA alone. Fourteen studies [10 salmeterol/fluticasone and 4 formoterol/budesonide] met the inclusion criteria, randomising 11,794 people with severe COPD. There was low quality evidence that exacerbation rates in people using LABA/ICS inhalers were lower in comparison to those with LABA alone, from nine studies which randomised 9,921 patients [rate ratio 0.76; 95% CI 0.68 to 0.84]. There was a high statistical heterogeneity between the results of the studies as well as a risk of bias from the high withdrawal rates across the studies. There was no significant difference in the rate of hospitalisations and in mortality between patients on combination therapy or with LABA alone.

The combination was more effective than LABA alone in improving SGRQ, TDI, COPD symptoms and lung function parameters, but the reviewers expressed doubts concerning the clinical relevance of the differences in outcome [200].

Formoterol/budesonide vs other comparators

The combination was more effective than budesonide monotherapy [202] and as effective as oral prednisolone [202].

A US administrative claims database study showed no differences between formoterol/budesonide [n = 3,788] and salmeterol/fluticasone [n = 6,439] in the incidence of exacerbations or COPD-related hospitalisations [203].

Glycopyrronium/Indacaterol

Placebo-controlled studies

Three studies compared the combination to placebo, showing positive effects on lung function parameters and exercise tolerance [204-206].

Glycopyrronium/indacaterol vs glycopyrronium or indacaterol

The combination was compared to indacaterol or both constituents in three studies. The combination was consistently more effective regarding lung function parameters, TDI focal score and use of rescue medication. No significant differences became apparent

regarding SGRQ [65-67]. One study showed a reduction in exacerbations compared to glycopyrronium [67].

Glycopyrronium/indacaterol vs tiotropium

The combination was compared to tiotropium in three studies. The effects on studied endpoints, such as lung function parameters, SGR, TDI and rescue medication were similar for both medicines [66-68]. One study showed more favourable effects on FEV1 and patient-reported dyspnoea for the combination [68].

Another study demonstrated non-inferiority for glycopyrronium/indacaterol compared with tiotropium plus formoterol [71].

Glycopyrronium/indacaterol vs umeclidinium/vilanterol

The combinations were compared in two randomised, controlled, cross-over studies. The purpose was to demonstrate non inferiority of glycopyrronium/indacaterol. This goal was not met, although no clinically relevant differences in any lung function parameter were found [72].

Glycopyrronium/indacaterol vs salmeterol/fluticasone

The combinations were compared in three studies. Glycopyrronium/indacaterol showed significantly better effects on FEV1 and a [marginally] significant reduction of severe exacerbations, but similar effects on other parameters such as SGRQ, TDI and rescue medication use in one study [69]. The other study also showed more favourable effects on lung function parameters, TDI and rescue medication use, but not on SGRQ [70].

The largest study [Flame] investigated the effects of the combinations on exacerbation frequency. Glycopyrronium/indacaterol resulted in a significantly lower incidence of the annual exacerbation rate [3.59 vs 4.03], a longer time to the first exacerbation [71 days vs 51 days] and a lower frequency of moderate to severe exacerbations [0.98 vs 1.19]. The times to the first moderate to severe exacerbation or the first severe exacerbation was also significantly longer for glycopyrronium/indacaterol [73].

The combination was as effective when given in one container or in separate containers [207].

Olodaterol/Tiotropium

Comparison with individual components

The combination was more effective in improving lung function tests and SGRQ total scores than the individual components [75,208-210].

Comparison with salmeterol/fluticasone

The combination olodaterol/tiotropium was more effective in improving lung function tests than salmeterol/fluticasone [211].

Comparison with vilanterol/umeclidinium

The combination olodaterol/tiotropium was less effective than vilanterol/umeclidinium regarding trough FEV1 at 8 weeks [76].

Salmeterol/Fluticasone

Comparison with individual components

The combination was significantly more effective in improving lung function tests and quality of life than the individual components [81-88].

The effects on exacerbation rates compared to salmeterol were not completely consistent. An advantage was found in most [81,86,87,92], but not all studies [83].

Pharmacoepidemiological data show that salmeterol/fluticasone has a favourable effect on the mortality of COPD patients [212]. In another epidemiologic study a significant decline in mortality was seen in users of salmeterol/fluticasone [n = 866], inhaled corticosteroid + long-acting bronchodilator [n = 525], corticosteroid [n = 742] and long-acting bronchodilator alone [n = 531] in comparison with a short-acting bronchodilator alone [n = 1932]. The corrected hazard ratios were: 0.61; 0.59; 0.76 and 0.75 in comparison with a short acting bronchodilator [213].

These results could not be fully confirmed in a randomised study. The Torch study investigated effects of the combination, its components and placebo on mortality in a large group of COPD patients for 3 years. All-cause mortality rates were 12.6% for the combination, 15.2% for placebo, 13.5% in the salmeterol group and 16.0% in the fluticasone group. None of the differences reached statistical significance. The combination reduced the incidence of moderate or severe exacerbations [compared to components and placebo] and severe exacerbations [requiring hospitalisation] significantly compared to placebo [81]. In sub studies a significant reduction in mortality was seen versus placebo in patients with GOLD stage II, but not for stages III and IV [214]. The decline in lung function over 3 years was less pronounced for the combination than for placebo [215].

A Cochrane meta-analysis [2013] compared combinations of LABA and inhaled corticosteroids to placebo. Nineteen studies

were included with over 10,000 participants. Compared with placebo, both fluticasone/salmeterol and budesonide/formoterol reduced the rate of exacerbations. Mometasone/formoterol reduced the number of participants experiencing one or more exacerbation. Pooled analysis of the combined therapies indicated that exacerbations were less frequent when compared with placebo [Rate Ratio 0.73], corresponding to a reduction of one exacerbation every two to four years in these individuals. An overall reduction in mortality was seen, but this outcome was dominated by the results of one study [TORCH] of fluticasone/salmeterol. Further longer studies on budesonide/formoterol are required to clarify whether this is seen more widely. When a baseline risk of death of 15.2% from the placebo arm of TORCH was used, the three-year number needed to treat with fluticasone/salmeterol to prevent one extra death was 42 [with a huge 95% CI of 24 to 775]. All three combined treatments led to statistically significant improvement in health status measurements, although the mean differences observed were relatively small [216].

No differences regarding clinical efficacy were found between salmeterol/fluticasone delivered by Diskus or as MDI [217], as separate inhaler or in one inhaler [187], or by Diskus or Rotahaler [218].

Salmeterol/fluticasone was more effective than ipratropium/salbutamol [219] and theophylline [220] regarding lung function parameters.

Umeclidinium/Vilanterol

Placebo-controlled studies

The combination was more effective than placebo in improving health-related quality of life [221].

Comparison with individual components

The combination was more effective in improving lung function tests than the individual components. Effects on TDI and SGRQ and exercise endurance were also superior to umeclidinium and vilanterol separately. No significant differences in the effect on exacerbations were found, however [90-94].

Comparison with tiotropium

The combination was more effective in improving lung function tests, TDI and SGRQ than tiotropium in two direct comparative studies [94,95].

Comparison with tiotropium/olodaterol

The combination umeclidinium/vilanterol was non inferior to tiotropium/olodaterol in a per protocol population and superior in an intent-to-treat analysis regarding the primary endpoint [FEV1 change at 8 weeks] [76].

Comparison with salmeterol/fluticasone

Umeclidinium/Vilanterol was more effective than salmeterol/fluticasone regarding effects on lung function tests. Results were less conclusive regarding effects on TDI and SGRQ [96].

Vilanterol/fluticasone furoate

Placebo-controlled studies

The combination was more effective than placebo in improving lung function in two studies [222,223].

Comparison with individual components

The combination was more effective in improving lung function tests than the individual components [97-99].

Two large scale studies compared 3 combinations [25/50, 25/100 and 25/200 mcg of vilanterol and fluticasone furoate] to vilanterol monotherapy [25 mcg] regarding the incidence and severity of exacerbations of COPD. The results were combined in one publication. The rate of moderate and severe exacerbations was decreased in patients with a history of such exacerbations, but not in patients without previous exacerbations in one study and a decreased incidence of moderate to severe exacerbations was found in the whole study population in study 2 [100].

A large scale [N = 23,835] study investigated the effects of the combination, its components and placebo on overall mortality in patients with COPD with heightened cardiovascular risk. The average study duration was three years. No significant difference was seen between the combination or its components and placebo regarding all-cause mortality or any other mortality of cardiovascular morbidity endpoint [103].

Comparison with salmeterol/fluticasone

Vilanterol/fluticasone furoate was more effective than salmeterol/fluticasone twice daily regarding effects on lung function tests in four studies, summarised in two publications 101, 102].

Real life study

One British study compared vilanterol/fluticasone with usual

care in a randomised manner in 75 general practices, including 2799 patients with COPD. The primary endpoint was the rate of moderate to severe exacerbations among patients who had an exacerbation within one year before the trial. The rate of moderate or severe exacerbations was significantly lower by 8.4% with the combination than with usual care [224].

Triple combinations

Beclomethasone/formoterol/glycopyrronium

The triple combination was compared to budesonide/formoterol in the Trilogy study. Pre-dose and 2 hours post dose FEV₁ were significantly improved by the triple combination. Adjusted annual exacerbation frequencies were also improved by the triple combination: 0.41 vs 0.53, corresponding to a 23% reduction [104].

The fixed triple combination was compared to an open combination of the same components and to tiotropium in the Trinity study. The fixed and open triple combinations showed similar efficacy and safety, whereas a lower moderate to severe exacerbation rate was found compared to tiotropium [0.46 vs 0.57 per year] [105].

The Tribute study compared the triple combination to indacaterol plus glycopyrronium. Moderate to severe exacerbation rates were significantly higher for the dual combination: 0.50 per year vs 0.59 per year [106]. It should be noted that the absolute difference between both combinations was small: 0.09 exacerbations per year.

Fluticasone furoate/umeclidinium/vilanterol

The triple combination was compared to budesonide/formoterol in the FULFIL trial. Pre-dose FEV₁ was significantly improved by the triple combination. Adjusted annual exacerbation frequencies were also improved by the triple combination, corresponding to a 35% reduction [107].

The IMPACT study compared the triple combination with fluticasone furoate plus vilanterol and the combination of vilanterol and umeclidinium. The study details are summarised in the Tables. The study duration was 1 year and the primary endpoint was the annual rate of moderate to severe exacerbations. All combinations were given in the Ellipta inhaler. The rate of moderate to severe exacerbations was significantly lower for the triple combination compared to the LABA/ICS combination [Rate ratio 0.85, 95% CI

0.80-0.90]. The rate ratio compared to the LABA/LAMA combination was 0.75, 95% CI 0.70-0.81]. All patients in the study suffered at least one moderate to severe exacerbation in the year prior to the study. The difference in the annual exacerbation rate was also statistically significantly lower in the triple combination in those patients who had experienced at least 2 exacerbations per year prior to the study: 11% and 28% lower rate ratio [108].

There are no indications of major differences in clinical efficacy between the various compounds within the therapeutic classes [LABA, LAMA etc]. All medicines are awarded 70%. It should be noted that different classes are used for different patient categories.

Safety

LABA

Formoterol

Two placebo-controlled studies investigated the cardiac safety of formoterol [Aerolizer]. Neither study showed negative cardiac effects compared to placebo. Studies comparing formoterol [Aerolizer] to ipratropium bromide or theophylline also showed a good tolerability profile [225-227].

The side-effects profile of Aerolizer and Nexthaler were similar in a direct comparative study [228].

Indacaterol

A Cochrane meta-analysis on all available studies, which included 13 multicenter RCTs randomly assigning over 9,600 participants with stable COPD was published early 2015 [141].

Nine trials contributed data on serious adverse events with indacaterol and placebo. No statistically significant difference in the incidence of serious adverse events or mortality was noted for [any dose level of] indacaterol and placebo. The confidence intervals were however too wide to rule out clinically important differences in serious adverse events between indacaterol and formoterol or salmeterol [141].

Four trials with active controls contributed data on serious adverse events. Dosages of 150 mcg, 300 mcg and 600 mcg indacaterol were compared to formoterol and salmeterol. No statistically significant difference in serious adverse events was reported between each dose of indacaterol and both active comparators. The confidence intervals were however too wide to rule out clinical

cally important differences in serious adverse events between indacaterol and formoterol or salmeterol [141].

No differences were found in the cardio- and cerebrovascular safety of indacaterol compared to placebo, formoterol, salmeterol and tiotropium [229]. Indacaterol has no relevant effects on QTc interval in dosages of up to 600 mcg [230].

The number of deaths adjusted per patient year was lower than with placebo [231].

Olodaterol

A pre-specified pooled analysis of the large scale comparative studies between olodaterol and formoterol in the whole population and in subgroups with cardiac disease. Fatal adverse events occurred in similar frequency for olodaterol 5 mcg [1.5%], olodaterol 10 mcg [1.9%], formoterol [2.2%] and placebo [1.5%]. The most frequent complication was COPD exacerbation, followed by cardiac complications. The incidence of cardiovascular adverse events was similar for all groups [5%, 5%, 4% and 7%, respectively], both in the whole population as in the subpopulation with cardiac history at baseline [16%, 14%, 13% and 11%, respectively] [232].

Olodaterol did not affect mortality in patients with COPD and had no significant impact on nonfatal serious adverse events compared to placebo [233].

No significant differences were observed between olodaterol and formoterol regarding the incidence of serious adverse events [234].

Salmeterol

In the POET study, the incidence of respiratory, thoracic and mediastinal events was significantly higher for salmeterol compared to tiotropium, which was mainly caused by the lower incidence of exacerbations for tiotropium [see section on efficacy]. Pneumonia was seen in a similar frequency for both medicines. No significant differences in fatal adverse events was seen between salmeterol and tiotropium [97].

LAMA

Acclidinium

A Cochrane meta-analysis was performed on all available acclidinium studies, which included 12 multicenter RCTs randomly assigning over 9,500 participants with stable COPD. Acclidinium

non-significantly decreased cerebrovascular events compared to placebo [OR 0.58; 95% CI 0.25 to 1.33] [116].

The Ascent COPD study compared acclidinium and placebo in 3630 patients with moderate to very severe COPD and either a history of cardiovascular disease or at least 2 atherothrombotic risk factors, follow-up occurred for up to 3 years. The primary safety endpoint was time to first MACE over up to 3 years. 69[3.9%] acclidinium and 76 [4.2%] placebo patients had a MAC [Ac1].

Glycopyrronium

Placebo controlled studies showed no significant differences in the incidence of adverse events between glycopyrronium and placebo [130-134]. One large scale study [GLOW1] also investigated effects on QTc interval. A higher incidence of QTc interval prolongation was found for glycopyrronium than for placebo, but it was not stated whether that difference was statistically significant [132].

An analysis of comparative studies between glycopyrronium [n = 1075] and tiotropium [n = 267] showed a very similar tolerability profile. Serious adverse events were seen in 10.4% of patients treated with glycopyrronium vs 15.4% for tiotropium. It was not stated whether this represented a significant difference. The incidence of ECG abnormalities [QTc interval prolongation] was comparable. A QTc increase of 30-60 msec was seen in 13.2% and 16.2% and an increase of > 60 msec in 0.6% and 0% of patients treated with glycopyrronium and tiotropium respectively [235].

Glycopyrronium and indacaterol were well tolerated in a comparative study of one year duration [236].

Tiotropium

An analysis [performed by the manufacturer of tiotropium] of pooled data from placebo-controlled trials showed a significantly lower incidence of adverse events [RR 0.90] and serious adverse events [RR 0.94] for tiotropium [Handihaler or Respimat] than for placebo [237].

A Cochrane meta-analysis has been performed [in 2013] comparing tiotropium to long acting beta-agonists [LABA] in the maintenance treatment of COPD. Seven clinical studies [12,223 patients with COPD] were included in the review. There was a significantly lower rate of non-fatal serious adverse events recorded with tiotropium compared with LABA [OR 0.88]. The tiotropium group was also associated with a lower rate of study withdrawals [OR 0.89] [178].

There has been extensive debate on the cardiovascular safety of tiotropium Respimat. The large scale Uplift study showed a numerical reduction in mortality in the tiotropium [Handihaler] group compared to placebo, but this did not reach statistical significance [174]. Concern was raised by a meta-analysis of studies using the Respimat device [238]. This meta-analysis, which included 5 randomised studies of 12 to 52 weeks duration [only 2 peer reviewed publications], demonstrated a 52% increase in mortality compared to placebo: 90 of 3,686 subjects treated with tiotropium versus 47 of 2,836 treated with placebo, $p=0.02$. An increased mortality was found for both the 5 and 10 mcg dose of tiotropium. Concern was strengthened by a database study, which showed a 27% increased risk of dying using tiotropium Respimat compared to Handihaler [95% confidence interval 1.03-1.57], with a marked increase in the risk of cerebrovascular death [HR 1.56]. No increased mortality was seen in patients without existing cardiovascular disease [239]. Shortly afterwards, the results of the TIOSPIR study were presented. This study compared tiotropium Respimat and Handihaler in a large population of COPD patients [17,135 subjects] with a follow-up of 2.3 years. The safety profile of tiotropium administered by Respimat [2.5 and 5 mcg dosages] and 18 mcg administered by Handihaler was similar. Risk of death was also similar. The hazard ratio for the 2.5 mcg dose was 0.96 [95% CI 0.84-1.09] and for the 5 mcg dosage 1.00 [95% CI 0.87-1.14]. The authors did not find an increased mortality in the subgroup of 1221 patients with existing cardiovascular disease at baseline. Patients with unstable cardiovascular conditions were however excluded from the study. Cardiovascular safety in the whole study population was also similar in the 3 groups [240].

A more recent population-based cohort study did not show differences in cardiovascular safety between tiotropium Respimat and Handihaler [241].

LABA/LAMA combinations

Glycopyrronium/indacaterol

A pooled safety analysis of comparative studies with the combination showed no negative effects compared with placebo for death, cardiovascular or cerebrovascular complications, pneumonia and atrial flutter or – fibrillation [242].

Umeclidinium/Vilanterol

The effects of umeclidinium and the combination with vilanterol on QTc interval were comparable to placebo [243].

LABA/ICS combinations

Formoterol/budesonide

A US administrative claims database study showed no differences between formoterol/budesonide [n = 3,788] and salmeterol/fluticasone [n = 6,439] in the incidence of pneumonia [203].

A Cochrane meta-analysis has been performed [in 2014] investigating the risk of pneumonia in patients using inhaled corticosteroids. The authors found 43 studies [26 fluticasone, 17 budesonide]. Evidence from the budesonide studies was more inconsistent and less precise, and budesonide studies were of shorter duration. A high dropout number was found, but this did not affect overall conclusions. Fluticasone increased non-fatal serious adverse pneumonia events [requiring hospital admission] [odds ratio [OR] 1.78; which represents 18 more cases per 1000 patients treated over 18 months. There was no evidence that suggested that this outcome would be different by combining fluticasone with salmeterol or vilanterol. Budesonide increased non-fatal serious adverse pneumonia events compared to placebo as well, but the effect was less precise and was based on shorter trials [OR 1.62]. An indirect comparison of budesonide versus fluticasone monotherapy revealed no significant differences with respect to serious adverse events or mortality. No significant difference in overall mortality rates was observed between either of the inhaled steroids and the control interventions [both high-quality evidence], and pneumonia-related deaths were too rare to permit conclusions to be drawn [244].

An analysis of studies with budesonide did not show an increased risk of pneumonia compared to non-users of budesonide [245].

Salmeterol/fluticasone

The large scale Torch study compared the combination to its components and placebo, The general tolerability profile was similar for the 4 treatment arms. The treatments containing fluticasone showed a higher incidence of pneumonia [19.6% for the combination; 18.3% for fluticasone; 13.3% for salmeterol and 12.3% for placebo]. No differences were seen in the incidence of fractures or cardiac events [81].

The Summit study did not show an increased risk of pneumonia [246].

The incidence of pneumonia for fluticasone users has been studied extensively. These studies are not easy to interpret because of differences in the definition/diagnosis of pneumonia in studies performed with individual inhaled corticosteroids. This makes it complex to use these studies for meta-analysis purposes [247]. A higher incidence of pneumonia for fluticasone propionate [FP] was found in several analyses [247-250]. The relatively high dosage of FP in patients with COPD might play a role in this. Fluticasone furoate [FF] is used at a lower dose, also when corrected for potency. On the other hand, the EMA concluded that there were no relevant differences in the incidence of pneumonia for individual corticosteroids in COPD [251].

Comparison with individual components

The combination as well tolerated as the individual components [VF1, VF2].

Two large scale studies compared 3 combinations [25/50, 25/100 and 25/200 mcg of vilanterol and fluticasone furoate] to vilanterol monotherapy [25 mcg]. The overall tolerability profile was comparable in the treatment arms, but a higher incidence of pneumonia was found in the combination arms [3%] vs monotherapy [1%]. Fractures also occurred more frequently with the combination than with monotherapy: 2% vs 1% [100].

The combination vilanterol and fluticasone furoate was not associated with prolongation of the QTc interval [243].

The IMPACT study compared the triple combination of fluticasone furoate, umeclidinium and vilanterol with fluticasone furoate plus vilanterol and the combination of vilanterol and umeclidinium. The study details are summarised in the tables. The study duration was 1 year. All combinations were given in the Ellipta inhaler. A higher incidence of pneumonia was observed in the inhaled corticosteroids groups compared to the LABA/LAMA group: 8% vs 5% [108].

There are no relevant differences in safety of monotherapies and combinations of LABA and LAMA. All medicines are awarded 80%.

There is a higher incidence of pneumonia for combinations including inhaled corticosteroids. These are awarded 70%. Combinations using fluticasone propionate were scored 5% lower because of its relatively high incidence of pneumonia. These were scored 65%.

Tolerability

Acclidinium

A Cochrane meta-analysis was performed on all available acclidinium studies, which included 12 multicentre RCTs randomly assigning over 9,500 participants with stable COPD. There was no significant difference between acclidinium and placebo or tiotropium for the anticholinergic side effect of dry mouth. Diarrhoea was found to be significantly increased with acclidinium [once daily therapy] compared to placebo [OR 2.32; 95%CI 1.14 to 4.74; 2 trials, 1647 participants]. However, no statistical difference was observed between once daily and twice daily acclidinium. Other reported adverse events such as nasopharyngitis, headache, cough, hypertension, respiratory tract infections, urinary tract infections, fatigue, dizziness, dyspnoea, arthralgia, back pain and oropharyngeal pain showed no significant difference between acclidinium and placebo or tiotropium in the pooled analysis [116].

Formoterol

A number of placebo-controlled studies was performed with either the Turbuhaler or Aerolizer device of formoterol. No significant differences in tolerability were observed in these studies, involving over 1,000 patients [118-123].

No differences in the tolerability profile of formoterol and tiotropium were found in a direct comparative study [44].

The tolerability profiles of formoterol and olodaterol were similar in four comparative studies [54,55].

Studies comparing formoterol to the combination formoterol/budesonide or formoterol/beclomethasone showed no relevant differences in tolerability [51].

Glycopyrronium

Placebo controlled studies showed no significant differences in the incidence of adverse events between glycopyrronium and placebo [130-136].

An analysis of comparative studies between glycopyrronium [n = 1075] and tiotropium [n = 267] showed a very similar tolerability profile [235].

Olodaterol

The tolerability profile of olodaterol was comparable to placebo, formoterol and tiotropium in randomised controlled clinical trials [54,55,74,147].

Salmeterol

The tolerability profile of salmeterol was comparable to placebo in controlled studies [148-152].

Tiotropium

Tiotropium was well tolerated in placebo-controlled trials. The incidence and severity of adverse events were comparable to placebo [158-172]. Dry mouth was observed more frequently for tiotropium than for placebo [237,252,253].

Umeclidinium

Umeclidinium was well tolerated. The incidence of adverse events was comparable to placebo [194].

Acridinium/formoterol

Two studies compared the acridinium/formoterol combinations 400/6 mcg and 400/12 mcg bid to the individual components. No statistically significant differences were observed in the incidence of adverse events between the comparators [40,41]. These results were similar at longer follow-up [43].

Formoterol/beclomethasone

Studies comparing formoterol/beclomethasone to formoterol, to formoterol/budesonide or to salmeterol/fluticasone showed no relevant differences in tolerability [51-53].

Formoterol/budesonide

Studies comparing formoterol to the combination formoterol/budesonide or formoterol/beclomethasone showed no relevant differences in tolerability [51].

Glycopyrronium/indacaterol

The combination was well tolerated in clinical trials with few, if any, differences with placebo or the individual components of the combination. Large scale comparative studies with tiotropium and salmeterol/fluticasone did not show major differences in tolerabil-

ity or safety [65-71].

Olodaterol/tiotropium

The combination was well tolerated in clinical trials. The incidence and severity of adverse events was comparable to the individual components [75, 209].

Umeclidinium/Vilanterol

Umeclidinium/Vilanterol was well tolerated. The incidence of adverse events was comparable to the individual components, tiotropium and salmeterol/fluticasone [90-96,221].

Comparison with individual components

The combination as well tolerated as the individual components [97,98].

Comparison with salmeterol/fluticasone

The tolerability profile of vilanterol/fluticasone furoate was comparable to salmeterol/fluticasone twice daily in four studies, summarised in two publications [101,102].

There are no relevant differences in the tolerability profiles of the formulations. All medicines are awarded 80%.

Dosage frequency

The dosage frequency as indicated in the SPC's is as follows: Formoterol, Salmeterol, acridinium [and combination] and the triple combination beclomethasone/formoterol/glycopyrronium are given twice daily and score 80%.

The other medicines/combinations are given once daily and are awarded 100%.

Documentation [clinical studies]

The documentation [clinical studies] is as follows.

| Medicine | Studies | Patients | Score | Refs |
|----------------|---------|----------|-------|---|
| LABA: | | | | |
| Formoterol | >20 | >1000 | 100% | [44-51,118-123,199-202,225-227,253,254] |
| Indacaterol | 16 | >1000 | 90% | [59-66,138-144,236] |
| Olodaterol | 8 | >1000 | 70% | [54,55,71,146,147] |
| Salmeterol | 16 | >1000 | 90% | [62,63,81-88,148,187,217-220] |
| LAMA | | | | |
| Acridiniums | 12 | >1000 | 80% | [38-43,109-115] |
| Glycopyrronium | 14 | >1000 | 85% | [56-58,66,67,130-137,236] |
| Tiotropium | >20 | >1000 | 100% | [38,39,56-61,66-68,74,77-80,89,94,95,105,158-170-174,188,190-192,209,210,240] |

| | | | | |
|--|----|-------|-----|---|
| Umeclidinium | 10 | >1000 | 75% | [89-95,193,194,221] |
| Combinations of two bronchodilators: | | | | |
| Acclidinium/formoterol | 5 | >1000 | 63% | [40-43,196] |
| Glycopyrronium/indacaterol | 14 | >1000 | 85% | [65-73,204-207,242] |
| Olodaterol/tiotropium | 5 | >1000 | 63% | [75,76,209-211] |
| Umeclidinium/vilanterol | 14 | >1000 | 70% | [72,76,90-96,108,221] |
| Combinations of bronchodilators and inhaled corticosteroids: | | | | |
| Formoterol/beclomethasone | 0 | 0 | 0% | |
| Formoterol/budesonide DPI | 5 | >1000 | 63% | [46-48,51,107] |
| Salmeterol/fluticasone propionate | 16 | >1000 | 90% | [42,52,64,69,70,81-84,85-88,96,101,102,218] |
| Vilanterol/fluticasone furoate | 10 | >1000 | 75% | [108,97-103,222,223] |
| Triple combinations | | | | |
| Beclomethasone/formoterol/glycopyrronium | 3 | >1000 | 54% | [104-106] |
| Fluticasone furoate/umeclidinium/vilanterol | 2 | >1000 | 55% | [107,108] |

Table B

Documentation [clinical experience]

The number of patient days is an estimation as limited published data are available on this topic.

The documentation [clinical experience] is as follows

[Table c]

Discussion and Conclusion

Score.

| Medicine | Years | Patient days (millions) | Score |
|--------------------------------------|-------|-------------------------|-------|
| LABA: | | | |
| Formoterol | >10 | >100 | 100% |
| Indacaterol | >10 | 50 | 75% |
| Olodaterol | 7 | 30 | 50% |
| Salmeterol | >10 | >100 | 100% |
| LAMA | | | |
| Acclidinium | 7 | 30 | 50% |
| Glycopyrronium | >10 | 40 | 70% |
| Tiotropium | >10 | >100 | 100% |
| Umeclidinium | 8 | 50 | 65% |
| Combinations of two bronchodilators: | | | |
| Acclidinium/formoterol | 6 | 25 | 43% |
| Glycopyrronium/indacaterol | >10 | 30 | 65% |
| Olodaterol/tiotropium | 7 | 25 | 48% |
| Umeclidinium/vilanterol | 8 | 40 | 60% |

| | | | |
|--|-----|------|------|
| Combinations of bronchodilators and inhaled corticosteroids: | | | |
| Formoterol/beclomethasone | >10 | >100 | 100% |
| Formoterol/budesonide DPI | >10 | >100 | 100% |
| Salmeterol/fluticasone propionate | >10 | >100 | 100% |
| Vilanterol/fluticasone furoate | 7 | 50 | 60% |
| Triple combinations | | | |
| Beclomethasone/formoterol/glycopyrronium | >10 | 3 | 65% |
| Fluticasone furoate/umeclidinium/vilanterol | 7 | 5 | 60% |

| Criterion | Indications | Interactions | Efficacy | Safety | Tolerability | Dosage frequency | Documentation | Score |
|---|-------------|--------------|----------|--------|--------------|------------------|---------------|-------|
| Weight | 50 | 50 | 500 | 150 | 100 | 80 | 70 | 1000 |
| Medicine | | | | | | | | |
| Monotherapy: | | | | | | | | |
| LABA | | | | | | | | |
| Formoterol | 50 | 40 | 350 | 120 | 80 | 72 | 70 | 782 |
| Indacaterol | 35 | 40 | 350 | 120 | 80 | 80 | 58 | 763 |
| Olodaterol | 35 | 40 | 350 | 120 | 80 | 80 | 43 | 748 |
| Salmeterol | 50 | 35 | 350 | 120 | 80 | 64 | 67 | 766 |
| LAMA | | | | | | | | |
| Acclidinium | 35 | 40 | 350 | 120 | 80 | 64 | 46 | 735 |
| Glycopyrronium | 35 | 40 | 350 | 120 | 80 | 80 | 55 | 760 |
| Tiotropium | 35 | 40 | 350 | 120 | 80 | 80 | 70 | 775 |
| Umeclidinium | 35 | 40 | 350 | 120 | 80 | 80 | 49 | 754 |
| Combinations of two bronchodilators: | | | | | | | | |
| Acclidinium/formoterol | 35 | 35 | 350 | 120 | 80 | 64 | 37 | 721 |
| Glycopyrronium/indacaterol | 35 | 35 | 350 | 120 | 80 | 80 | 53 | 753 |
| Olodaterol/tiotropium | 35 | 35 | 350 | 120 | 80 | 80 | 39 | 739 |
| Umeclidinium/vilanterol | 35 | 35 | 350 | 120 | 80 | 80 | 45 | 745 |
| Combinations of bronchodilators and inhaled corticosteroids: | | | | | | | | |
| Formoterol/beclomethasone | 50 | 35 | 350 | 105 | 80 | 64 | 35 | 719 |
| Formoterol/budesonide | 50 | 30 | 350 | 105 | 80 | 64 | 57 | 736 |
| Salmeterol/fluticasone propionate | 50 | 30 | 350 | 98 | 80 | 64 | 67 | 739 |
| Vilanterol/fluticasone furoate | 50 | 35 | 350 | 105 | 80 | 80 | 44 | 744 |
| Triple combinations | | | | | | | | |
| Beclomethasone/formoterol/glycopyrronium | 35 | 35 | 350 | 105 | 80 | 64 | 19 | 711 |
| Fluticasone furoate/umeclidinium/vilanterol | 35 | 35 | 350 | 105 | 80 | 80 | 19 | 725 |

Discussion

Applied methodology

This was done by means of the SOJA method, which is a well-established rational and transparent way of selecting medicines within a therapeutic class from a formulary perspective.

Outcome

Only very limited differences in scores were found between the medicines within classes [LAMA, LABA, LABA/LAMA, LABA/ICS and triple combinations]. The highest and lowest scores were within a 5% margin.

Strength and limitations of the methodology

It should be taken into consideration that this analysis is limited to pharmacological aspects. In clinical practice, patient related factors play an important role, such as inhalation flow, hand-eye coordination and personal preferences of the patient.

The evaluation of criteria in the SOJA method is highly standardised in order to promote unbiased judgement of drugs from various pharmacotherapeutic categories based on clinically relevant criteria. There will always be room for debate whether or not the correct scoring system was used for each criterion and judgement may be arbitrary for most, if not all, criteria. This is the case with any method used to quantify properties of drugs. The SOJA method is intended as a tool for rational drug decision making, forcing clinicians and pharmacists to include all relevant aspects of a certain group of drugs, thereby preventing formulary decisions being based on only one or two criteria. Besides this, possible "hidden criteria" are excluded from the decision making process. The outcome of this study should be seen as the basis for discussions within formulary committees and not as an absolute truth.

Obviously, the score depends on the relative weight that is assigned to each individual selection criterion. Therefore an interactive program is available, which makes it easy for local and regional formulary committees to assign personal weights to each selection criterion by individual members of the committees. If a physician or pharmacist considers individual criteria as totally irrelevant, this criterion may be assigned 0 points, thereby ignoring this criterion.

There is extensive experience with the SOJA method, which made clear that almost all physicians and pharmacists assign a high

relative weight to clinical efficacy, safety and tolerability and ease of use. There were very limited differences between the individual medicines within each class.

Acquisition cost was not taken into account, because this varies with time. In practice acquisition cost is of course an important selection criterion, especially because there are very limited differences between the medicines from a clinical perspective. Exclusion of this criterion also makes this comparison more internationally applicable.

The device was not taken into consideration for the calculation of the scores. There are no relevant differences between the properties of the medicines. Therefore the Working Party decided that the selection of inhaled medication for COPD should be based on the properties of the devices, rather than on the properties of the medicines.

Conclusion

The scores for the individual medicines within each class of inhaled medicines were quite similar. This makes it logical to base formulary decisions on the properties of the devices. This analysis will be published in a separate article.

Conflicts of interest

None reported.

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