# Annex I

***List of the names, pharmaceutical forms, strengths of the medicinal products, route of administration, applicants and marketing authorisation holder in the Member States***

| Member State EU/EEA | Marketing authorisation holder | Applicant | (Invented) Name | Strength | Pharmaceutical form | Route of administration |
|---|---|---|---|---|---|---|
| Bulgaria | | Sanofi-Aventis Bulgaria EOOD<br>103, blvd Alexander Stamboliiski<br>1303 Sofia<br>Bulgaria | Actonel Combi D | 35 mg + 1000 mg/880 IU | film-coated tablets + effervescent granules | Oral use |
| France | | Procter & Gamble Pharmaceuticals France<br>163-165 Quai Aulagnier<br>92600 Asnières-sur-Seine<br>France | Norsedcombi | 35 mg + 1000 mg/880 IU | film-coated tablets + effervescent granules | Oral use |
| Germany | | Warner Chilcott Deutschland GmbH<br>Dr.-Otto-Röhm-Strasse 2-4<br>64331 Weiterstadt<br>Germany | Norsed plus Calcium D | 35 mg + 1000 mg/880 IU | film-coated tablets + effervescent granules | Oral use |
| Ireland | | Warner Chilcott UK Limited,<br>Old Belfast Road,<br>Millbrook, Larne, County Antrim,<br>BT40 2SH<br>United Kingdom | Optinate Plus Ca &D | 35 mg + 1000 mg/880 IU | film-coated tablets + effervescent granules | Oral use |
| Italy | | sanofi-aventis S.p.A.<br>viale Luigi Bodio, 37/B<br>20158 Milan<br>Italy | Opticalcio D3 | 35 mg + 1000 mg/880 IU | film-coated tablets + effervescent granules | Oral use |
| Sweden | sanofi-aventis S.p.A.<br>Viale Luigi Bodio, 37/b<br>20158 Milano<br>Italy | | Norsed Combi D | 35 mg + 1000 mg/880 IU | film-coated tablets + effervescent granules | Oral use |

# Annex II

## *Scientific conclusions and grounds for positive opinion*

# Scientific conclusions

## *Overall summary of the scientific evaluation of Norsed Combi D and associated names (see Annex I)*

Risedronate sodium is a bisphosphonate that inhibits bone resorption and has been shown to increase bone mass and biomechanical skeletal strength. Treatment with anti-resorptive agents such as bisphosphonates together with oestrogen replacement therapy can prevent or reduce the loss of bone associated with postmenopausal osteoporosis. Treatment with bisphosphonates generally also includes treatment with calcium, to support the remineralisation of the skeleton and with colecalciferol (vitamin $D_3$) which increases calcium absorption. The Applicant submitted an application for mutual recognition of the marketing authorisation granted by Sweden in 2006 for Norsed Combi D, a combination product consisting of risedronate sodium 35 mg film-coated tablets together with 1000 mg calcium carbonate and 880 IU colecalciferol effervescent granules. The procedure started in November 2009 and the indications applied for are the "*treatment of postmenopausal osteoporosis, to reduce the risk of vertebral fractures*" and the "*treatment of established postmenopausal osteoporosis, to reduce the risk of hip fractures*". Concomitant administration of calcium significantly impairs the absorption of risedronate and must therefore be avoided. Bisphosphonates maintain their activity for extended periods and as a result, do not need continuous dosing. Therefore, the proposed dosage is one risedronate tablet on day 1 followed by one sachet of calcium/colecalciferol daily for day 2 through to day 7, repeating this 7-day sequence each week.

A concerned member state (CMS) raised Potential Serious Risks to Public Health pertaining to the lack of evidence of efficacy; in particular regarding the claims of improved benefit compared to the individual products and improved compliance compared to standard treatment. The procedure was therefore referred to the CMD(h) and subsequently, to the CHMP under Article 29(4), in April 2010. The objecting CMS considered the benefit-risk balance of Norsed Combi D to be unfavourable and presented specific points for objection to the application.

## Data submitted by the Applicant

The CHMP noted the data submitted in the initial application. Module 2 contained the Quality Overall Summary together with the Clinical and Non Clinical overview and summary documents. Module 3 contained relevant documentation for the risedronate film-coated tablet as well as for the effervescent calcium-colecalciferol effervescent granules, for the drug substance as well as for the drug product. Module 4 contained three preclinical risedronate studies. The CHMP agreed that the pharmacology and toxicology of calcium and colecalciferol are well-established, that combinations of these two products have been used globally in clinical practice for many years, and that the human experience supersedes non-clinical data. Twenty-eight adequate non-clinical literature references were also submitted. Module 5 contained pivotal clinical studies and study reports for the 35 mg risedronate tablet and the calcium plus colecalciferol product as well as the pivotal study for approval of the weekly 35 mg risedronate tablet, in which patients were co-administered calcium and vitamin D, along with 46 relevant clinical literature references. In conclusion, the CHMP considered the Applicant to have submitted all relevant and necessary data to support a full dossier application under Article 8(3).

## Classification as an exceptional case

The CHMP considered the combination pack of risedronate and calcium plus colecalciferol to be an "exceptional case", based on the problematic dosing and the risk for interaction prohibiting concomitant intake as per the Guideline for combination products (CHMP/EWP/240/95).

## Public health benefit and improved compliance

According to the CHMP Guideline on combination products, "combination packs would only be acceptable in exceptional cases, when there would be clear public health benefits of the treatment regimen and/or compliance, taking into account the required justifications set-out in section 5 of this guideline". The CHMP was of the opinion that the combination pack will simplify the correct dosage regimen compared to the individual products, thereby reducing the risk of interactions. The CHMP considered this to be a clear public health benefit. On these grounds, the CHMP did not consider the demonstration of improved compliance to be an absolute requirement for the approval of this combination product.

In conclusion, the CHMP considered all the objections raised by the objecting concerned member to be adequately addressed and that they should not prevent the authorisation of the product. The CHMP was of the opinion that the application is approvable.

## *Grounds for positive opinion*

Whereas

- the data submitted in the initial authorisation application product file was considered to sufficiently support the marketing authorisation application,
- the CHMP was convinced of the clear public health benefits and improved compliance resulting from the this product,

the CHMP has recommended the granting of the marketing authorisations for which the summary of product characteristics, labelling and package leaflet remain as per the final versions achieved during the Coordination group procedure as mentioned in Annex III for Norsed Combi D and associated names (see Annex I).

# Annex III

***Summary of product characteristics, labelling and package leaflet***

The valid summary of product characteristics, labelling and package leaflet are the final versions achieved during the Coordination group procedure.