MINISTRY OF HEALTH

O R D E R

on amendment of Annexes I-III to Order of the Minister of Health no. 400/2006 on approval of Statements for use in the wording of package leaflet, summary of product characteristics and label information for medicinal products authorised for marketing in Romania

On seeing the approval report of the Direction on drug policy Cs. A. No. 12.385 of 24 November 2010,

Taking into account:

- the provisions of Title XVII „The Medicinal Products" of Law No. 95/2006 on healthcare reform, as amended;
- Government Decision No. 734/2010 related to the set up and functioning of the National Agency for Medicines and Medical Devices,

based on Government Decision No. 144/2010 on the organisation and functioning of the Ministry of Health, as amended,

the minister of health hereby issues the following order:

Art. I – Annexes I-III to Order of the Minister of Health no. 400/2006 on approval of Statements for use in the wording of package leaflet, summary of product characteristics and label information for medicinal products authorised for marketing in Romania, published in the Official Gazette of Romania, Part I, no. 355 of 20 April 2006, are amended and replaced with Annexes 1-3, which are integral parts of this Order.

Art. II – This Order is to be published in the Official Gazette of Romania, Part I.

Minister of health,

Cseke Attila

Bucharest, 24 November 2010.

No. 1.446

ANNEX 1

(Annex 1 to Order no. 400/2006)

Statements for use under section 4.6 – Pregnancy and lactation

of the Summary and Product Characteristics (SmPC)

With respect to „Pregnancy"

[1] <Based on human experience *[specify]* {Active substance} is suggested / suspected to cause congenital malformations *[specify]* when administered during pregnancy.

{Invented name} is contraindicated <during pregnancy><during pregnancy (trimester)> *[only in case of a strict contraindication]* (see section 4.3).

<Women of childbearing potential have to use effective contraception <during <and up to {number} weeks after> treatment.>>

[2] <Based on human experience *[specify]* {Active substance} is suggested / suspected to cause congenital malformations *[specify]* when administered during pregnancy.

A. <Animal studies do not indicate reproductive toxicity (see section 5.3).>

[sau]

B. <Animal studies are insufficient with respect to reproductive toxicity (see section 5.3).>

{Invented name} should not be used <during pregnancy><<during pregnancy (trimester)>, unless the woman's clinical state requires treatment with {active substance}.

<Women of childbearing potential have to use effective contraception <during <and up to {number} weeks after> treatment.>>

[3] <Based on human experience *[specify]* {Active substance} is suggested / suspected to cause congenital malformations *[specify]* when administered during pregnancy.

Studies in animals have not shown direct or indirect reproductive toxicity (see section 5.3).

{Invented name} should not be used <during pregnancy><<during pregnancy (trimester)>, unless the woman's clinical state requires treatment with {active substance}.

<Women of childbearing potential have to use effective contraception <during <and up to {number} weeks after> treatment.>>

[4] <Data related to the use of {active substance} in pregnant women are inexistent or limited.

A. <Animal studies do not indicate reproductive toxicity (see section 5.3).>

[or]

B. <Animal studies are insufficient with respect to reproductive toxicity (see section 5.3).>

{Invented name} should not be used <during pregnancy><<during pregnancy (trimester)> and in women of childbearing potential not using contraception.>

[5] <Data related to the use of {active substance} in pregnant women are inexistent or limited (less than 300 birth-related results).

Studies in animals have not shown direct or indirect reproductive toxicity (see section 5.3).

As a precautionary measure, it is preferable to avoid using {Invented name} <during pregnancy><during pregnancy (trimester)>.>

[6] <A moderate amount of data on pregnant women (between 300-1000 pregnancy outcomes) indicate no malformative or feto/ neonatal toxicity of {Active substance}.

A <Animal studies do not indicate reproductive toxicity (see section 5.3).>

[or]

B. <Animal studies are insufficient with respect to reproductive toxicity (see section 5.3).>

As a precautionary measure, it is preferable to avoid using {Invented name} <during pregnancy><during pregnancy (trimester)>.

[7] <A moderate amount of data on pregnant women (between 300-1000 pregnancy outcomes) indicate no malformative or feto/ neonatal toxicity of {Active substance}.

Studies in animals have not shown reproductive toxicity (see section 5.3).

Using {Invented name} <during pregnancy><during pregnancy (trimester)> may be considered, if required.

[8] <A large amount of data on pregnant women (more than 1000 pregnancy outcomes) indicate no malformative nor feto/ neonatal toxicity of {Active substance}.>

{Invented name} can be used <during pregnancy><during {trimester} of pregnancy> if clinically needed.

[9] <No effects during pregnancy are anticipated, since systemic exposure to {Active substance} is negligible.>

{Invented name} can be used during pregnancy. *[E.g. medicinal products for which negligible systemic exposure/negligible pharmacodynamic systemic activity has been demonstrated in clinical situation]*

With respect to „Lactation"

[1] <{Active substance}/metabolites are excreted in human milk and effects have been shown in breastfed newborns/infants of treated women.>

[or]

<{Active substance}/metabolites have been identified in breastfed newborns/infants of treated women. <The effect of {Active substance} on newborns/infants is unknown.> *[or]* <There is insufficient information on the effects of {Active substance} in newborns/infants.>>

[or]

<{Active substance}/metabolites are excreted in human milk to such an extent that effects on the breastfed newborns/infants are likely.>

<{Invented name}<is contraindicated during breast-feeding (see section 4.3)> *[or]* <should not be used during breast-feeding>.>

[or]

<Breast-feeding should be discontinued during treatment with {Invented name}.>

[or]

<A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from {Invented name} therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman.>

[2] <It is unknown whether {Active substance}/metabolites are excreted in human milk.>

[or]

<There is insufficient information on the excretion of {Active substance}/metabolites in human milk.>

[or]

<There is insufficient information on the excretion of {Active substance}/metabolites in animal milk.>

[or]

<Available pharmacodynamic/toxicological data in animals have shown excretion of {Active substance}/metabolites in milk (for details see 5.3).>

[or]

<Physico-chemical data suggest excretion of {Active substance}/metabolites in human milk.>

A risk to the newborns/infants cannot be excluded.

<{Invented name} <is contraindicated during breast-feeding (see section 4.3)> *[or]* <should not be used during breast-feeding>.>

[or]

<Breast-feeding should be discontinued during treatment with {Invented name}.>

[or]

<A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from {Invented name} therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman.>

[3] <No effects of {Active substance} have been shown in breastfed newborns/infants of treated mothers.>

[or]

<No effects on the breastfed newborn/infant are anticipated since the systemic exposure of the breast-feeding woman to {Active substance} is negligible.>

[or]

<{Active substance}/metabolites have not been identified in plasma of breastfed newborns/infants of treated mothers.>

[or]

<{Active substance}/metabolites are not excreted in human milk.>

[or]

<{Active substance}/metabolites are excreted in human milk, but at therapeutic doses of {Invented name} no effects on the breastfed newborns/infants are anticipated.>

{Invented name} can be used during breast-feeding.

ANNEX 2

(Annex II to Order no. 400/2006)

	RO
	[MedDRA frequency convention]
001	<Very common (≥1/10)>
002	<Common (≥1/100 şi <1/10)>
003	<Uncommon (≥1/1.000 şi <1/100)>
004	<Rare (≥1/10.000 şi <1/10.00)>
005	<Very rare (<1/10.000), unknown (cannot be estimated from the available data)>
	[MedDRA– system organ class database]
006	Infections and infestations
007	Neoplasms benign, malignant and unspecified (incl. cysts and polyps)
008	Blood and lymphatic system disorders
009	Immune system disorders
010	Endocrine disorders
011	Metabolism and nutrition disorders
012	Psychiatric disorders
013	Nervous system disorders
014	Eye disorders
015	Ear and labyrinth disorders
016	Cardiac disorders
017	Vascular disorders
018	Respiratory, thoracic and mediastinal disorders
019	Gastrointestinal disorders
020	Hepatobiliary disorders
021	Skin and subcutaneous tissue disorders
022	Musculoskeletal and connective tissue disorders
023	Renal and urinary disorders

024	Pregnancy, puerperium and perinatal conditions	**MedDRA**
025	Reproductive system and breast disorders	
026	Congenital, familial and genetic disorders	
027	General disorders and administration site conditions	
028	Investigations	
029	Injury, poisoning and procedural complications	
030	Surgical and medical procedures	
031	Social circumstances	

terminology to be used under section 4.8 – Adverse reactions of the Summary of Product Charactersitics (SmPC)

ANNEX 3

(Annex 3 to Order no. 400/2006)

Statements for use under: section 6.4 - Special precautions for storage, of the Summary of Product Characteristics (SmPC),

9 - Special storage conditions, of Labelling,

5 – Hot to store X, of the Package Leaflet

Summary of Product Characteristics

6.4 **Special precautions for storage**

<Do not store above <25°C> <30°C>> or

<Store below <25°C> <30°C>>

<Store in a refrigerator (2°C – 8°C)>

<Store and transport refrigerated (2°C – 8°C)>*

<Store in a freezer {temperature range}>

<Store and transport frozen {temperature range}>**

<Do not <refrigerate> <or> <freeze>>

<Store in the original <package>>

<Keep the {container} *** tightly closed>****

<Keep the {container} *** in the outer carton>****

<This medicinal product does not require any special storage conditions>

<This medicinal product does not require any special storage temperature.>*****

<in order to protect from <light> <moisture>>

A. **Labelling**

9. Special storage conditions

<Do not store above <25°C> <30°C>> or

<Store below <25°C> <30°C>>

<Store in a refrigerator>

<Store and transport refrigerated>*

<Store in a freezer>

<Store and transport frozen>**

<Do not <refrigerate> <or> <freeze>>

<Store in the original <package>>

<Keep the {container} *** tightly closed>****

<Keep the {container} *** in the outer carton>****

<in order to protect from <light> <moisture>>

B. **Package leaflet**

5. **How to store X**

Keep out of the reach and sight of children.

<Do not store above <25°C> <30°C>> or

<Store below <25°C> <30°C>>

<Store in a refrigerator (2°C – 8°C)

<Store and transport refrigerated (2°C – 8°C)>*

<Store in a freezer {temperature range}>

<Store and transport frozen {temperature range}>**

<Do not <refrigerate> <or> <freeze>>

<Store in the original <package>>****

<Keep the {container} *** in the outer carton>****

<Keep the {container} *** tightly closed>****

<This medicinal product does not require any special storage conditions>

<This medicinal product does not require any special storage temperature.>*****

<in order to protect from <light> <moisture>>

Do not use X after the expiry date which is stated on the <label> <carton> <bottle> <...>

<Do not use X if you notice {description of the visible signs of deterioration}.>

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* The stability data generated at 25°C/60%RH (acc) should be taken into account when deciding whether or not transport under refrigeration is necessary. The statement should only be used in exceptional cases.

** The statement should be used only when critical.

*** The actual name of the container should be used (e.g. bottle, blister etc.)

**** It should be stated whether the medicinal product is sensitive to light and/or moisture

***** Depending on the medicinal product's pharmaceutical form and properties, there is a product deterioration risk due to its physical changes, if the medicinal product is exposed to low temperatures. Moreover, low temperatures may have an impact upon the packaging, in certain cases. An additional specification may be required in order to consider this possibility.