DA	A
3.2.P.3.1 Manufacturers Manufacturer: ~~Glaxo Wellcome Production~~ ~~Zone Industrielle No. 2~~ ~~23, rue Lavoisier~~ ~~2700 Evreux~~ ~~France~~ ~~Secondary Packaging:~~ ~~GlaxoSmithKline Manufacturing S.p.A~~ ~~Via A. Fleming, 2~~ ~~37135 Verona~~ ~~Italy~~ ~~Or~~ ~~GlaxoSmithKline Manufacturing S.p.A~~ ~~Strada Provinciale Asolana, 90~~ ~~43056 San Polo di Torrile~~ ~~Parma~~ ~~Italy~~ ~~Testing:~~ ~~GlaxoSmithKline Manufacturing S.p.A~~ ~~Strada Provinciale Asolana, 90~~ ~~43056 San Polo di Torrile~~ ~~Parma~~ ~~Italy~~	**3.2.P.3.1 Manufacturers** **Manufacture, primary and secondary packaging, quality control testing and batch release:** **Losan Pharma GmbH** **Otto Hahn Strasse 13** **79395 Neuenburg am Rhein** **Germany**

5) variazione di tipo I n. B.II.a.1.a - Modifica o aggiunta di impressioni, rilievi o altre marcature compresa l'aggiunta o la modifica di inchiostri usati per marcare il medicinale. Modifiche di impressioni, rilievi o altre marcature:

Compresse 150 mg

DA	A
3.2.P.1.1 Descrizione Compresse di colore da bianco a giallo pallido, rotonde, piatte e con bordi smussati	**3.2.P.1.1 Descrizione** Compresse di colore da bianco a giallo pallido, rotonde, smussate, contrassegnate con la sigla "GS LHK" su un lato e piatte dall'altro

Compresse 300 mg

DA	A
3.2.P.1.1 Descrizione Compresse di colore da bianco a giallo pallido, rotonde, piatte e con bordi smussati	**3.2.P.1.1 Descrizione** Compresse di colore da bianco a giallo pallido, rotonde, smussate, contrassegnate con la sigla "GS MJG" su un lato e piatte dall'altro

6) variazione di tipo II n. B.II.a.3.b.2 - Modifiche nella composizione (eccipienti) del prodotto finito. Altri eccipienti. Modifiche qualitative o quantitative di uno o più eccipienti suscettibili di avere un impatto significativo sulla sicurezza, sulla qualità o sull'efficacia del medicinale:

Compresse 150 mg

DA

3.2.P.1.2 Composition

Ingredients	Quantity mg/tablet	Specification
Active Ingredient: Ranitidine Hydrochloride ~~(Granulated)~~	168.0*	~~BP/In house~~
Other Ingredients Monosodium citrate anhydrous	~~838.0~~	~~In House~~
Sodium Bicarbonate	~~834.0~~	PhEur
Aspartame	30.0	PhEur
Povidone K30	40.0	~~BP~~
Sodium Benzoate	~~60.0~~	PhEur
Orange Flavour 'IFF no 6'	20.0	In House
Grapefruit flavour 'IFF 18 C 222'	10.0	In House

* Equivalent to 150mg ranitidine base.

A

3.2.P.1.2 Composition

Ingredients	Quantity mg/tablet	Specification
Active Ingredient: Ranitidine Hydrochloride	168.0*	**PhEur**
Other Ingredients Monosodium citrate anhydrous	**818.0**	**PhEur**
Sodium Bicarbonate	**814.0**	PhEur
Aspartame	30.0	PhEur
Povidone K30	40.0	**PhEur**
Sodium Benzoate	**100.0**	PhEur
Orange Flavour 'IFF no 6'	20.0	In House
Grapefruit flavour 'IFF 18 C 222'	10.0	In House

* Equivalent to 150mg ranitidine base.

Compresse 300 mg

DA			A		
3.2.P.1.2 Composition			**3.2.P.1.2 Composition**		
Ingredients	**Quantity mg/tablet**	**Specification**	**Ingredients**	**Quantity mg/tablet**	**Specification**
Active Ingredient: Ranitidine Hydrochloride ~~(Granulated)~~	336.0*	~~BP/In House~~	Active Ingredient: Ranitidine Hydrochloride	336.0*	**PhEur**
Other Ingredients			Other Ingredients		
Monosodium citrate anhydrous	~~1222.4~~	~~In House~~	Monosodium citrate anhydrous	**1177.3**	**PhEur**
Sodium Bicarbonate	~~1216.6~~	PhEur	Sodium Bicarbonate	**1171.7**	PhEur
Aspartame	45.0	PhEur	Aspartame	45.0	PhEur
Povidone K30	60.0	~~BP~~	Povidone K30	60.0	**PhEur**
Sodium Benzoate	~~90.0~~	PhEur	Sodium Benzoate	**180.0**	PhEur
Orange Flavour 'IFF no 6'	30.0	In House	Orange Flavour 'IFF no 6'	30.0	In House
Grapefruit flavour 'IFF 18 C 222'	15.0	In House	Grapefruit flavour 'IFF 18 C 222'	15.0	In House
* Equivalent to 300mg ranitidine base.			* Equivalent to 300mg ranitidine base.		

7) variazione di tipo II n. B.II.b.3.b - Modifica nel procedimento di fabbricazione del prodotto finito. Modifiche importanti nel procedimento di fabbricazione della sostanza attiva, suscettibili di avere un impatto significativo sulla qualità, la sicurezza o l'efficacia del medicinale;

8) variazione di tipo I n. B.II.b.4.a Modifica della dimensione del lotto del prodotto finito. Sino a 10 volte superiore alla dimensione attuale approvata:

Compresse 150 mg

DA	A
3.2.P.3.2. Batch Formula	**3.2.P.3.2. Batch Formula**
~~450kg and 600kg~~	**850kg**

Compresse 300 mg

DA	A
3.2.P.3.2. Batch Formula	**3.2.P.3.2. Batch Formula**
~~450kg and 600kg~~	**829kg**

9) variazioni di tipo I n. B.II.b.5 - Modifica delle prove in corso di fabbricazione o dei limiti applicati durante la fabbricazione del prodotto finito:

DA

3.2.P.3.4 Control of Critical Steps and Intermediates

Dried granules

~~After drying check that the loss on drying at 60° C of the dried granules is ≯ 0.5% w/w.~~

Action limits applied to Zantac Effervescent Tablets during compression

Test	Limit	
	150mg	300mg
Mean weight	~~2.0g ± 2.5%~~	~~3.0g ± 2.5%~~
~~Weight uniformity~~	~~2.0g ± 5%~~	~~3.0g ± 5%~~
Thickness	~~4.0 to 4.3mm~~	~~4.7 to 4.9mm~~
~~Crushing strength~~	~~≥ 5.0~~	~~≥ 5.5~~
Disintegration time	~~≯ 3 minutes~~	~~≯ 3 minutes~~
Equilibrium relative humidity	~~≯ 30%~~	~~≯ 30%~~

The frequency of testing may vary depending on the compression machine and its normal operating speed (but will be at intervals not exceeding 60 minutes).

~~To assure uniformity of weight, twenty individual tablets are sampled and weighed regularly throughout the compression run. Crushing strength, disintegration time, thickness and equilibrium relative humidity of the tablets are measured regularly throughout the compression run.~~

Appropriate action will be taken as necessary to ensure that these tablet parameters do not fall outside permitted tolerances.

A

3.2.P.3.4 Control of Critical Steps and Intermediates

Granulation

Loss on drying 70°C/15 min **NMT 0.3%**

Equilibrium relative humidity **NMT 20%**

Blending

Yield effervescent granules **97-102%**

Final blend

Loss on drying 70°C/15 min **NMT 0.35%**

Equilibrium relative humidity **NMT 25%**

Compression

-150 mg Strength

Appearance **Round, flat bevel edged tablet; engraved "GS LHK"**

Colour **White to pale yellow**

Diameter **20 mm ± 0.3mm**

Height **4.0 – 4.4 mm**

Resistance to crushing **Not less than 60 N**

Disintegration **NMT 5 min**

Mean Weight **2.0 g ± 3% (mean)**

Uniformity of dosage units
- 2.0 g ± 5% (not less than 18 of 20)
- 2.0 g ± 10% (not less than 20 of 20)

	-300 mg Strength **Appearance** **Round, flat bevel edged tablet; engraved "GS MJG"** **Colour** **White to pale yellow** **Diameter** **23 mm ± 0.3mm** Height **4.7 – 5.1 mm** Resistance to crushing **Not less than 60 N** Disintegration **NMT 5 min** Mean Weight **3.0 g ± 3% (mean)** **Uniformity of dosage units** - 3.0 g ± 5% (not less than 18 of 20) - 3.0 g ± 10% (not less than 20 of 20) **Primary packaging** **Visual testing** **Clean, intact** **Coding batch number** **Corresponds** **Coding expiry date** **Corresponds** **Quality coding** **Legible** **Secondary packaging** **Primary units per finished pack** **Corresponds** **Leaflet** **Present** **Visual testing of finished package** **Clean, intact** **Coding batch number** **Corresponds** **Coding expiry date** **Corresponds** **Quality of coding** **Legible**

Inoltre, si esprime parere favorevole alla variazione di tipo I N1B/2010/4687:

Compresse 150 mg

DA

3.2.P.5.1 Specifications_Release

Test	**Limit**
Description	White to pale yellow, round, flat, bevel edged tablets
Test for identity by HPLC	The principal peak in the HPLC chromatogram of the sample corresponds with the peak produced by a reference standard of ranitidine hydrochloride
pH of solution	6.0 - 6.5
Disintegration time	Complies with the requirements of the European Pharmacopoeia
~~Uniformity of weight~~	~~Complies with the requirements of the European Pharmacopoeia~~
~~Water content (% w/w)~~	~~≯ 0.5~~
~~Residual solvents by GC (% w/w)~~	~~≯ 0.2~~
~~Related impurities by TLC (% w/w of nominal ranitidine content)~~ ~~Principal impurity~~ ~~Second impurity~~ ~~Total impurities~~	~~≯ 0.5~~ ~~≯ 0.3~~ ~~≯ 1.0~~
Ranitidine content by HPLC (% of label claim)	95 – 105

A

3.2.P.5.1 Specifications_Release

Test	**Limit**
Description[1]	White to pale yellow, round, bevelled tablet **marked "GS LHK" on one side and flat on the other**
Identity of Ranitidine Hydrochloride by HPLC **by UV**	 The principal peak in the HPLC chromatogram of the sample corresponds with the peak produced by a reference standard of ranitidine hydrochloride. **The UV spectrum obtained with the sample solution compares to that of the reference substance.**
pH of solution	6.0 - 6.5
Disintegration time	Complies with Ph.Eur. **NMT 5 minutes**
Uniformity of Dosage Units	**Complies with Ph.Eur.**
Loss on Drying	**NMT 0.5%***
Related impurities by HPLC (% w/w of nominal Ranitidine content) **RRT 0.66** **Any other impurity** **Total impurities**	 **NMT0.2** **NMT 0.2** **NMT 0.5**
Assay Ranitidine content by HPLC	95 – 105% L.S. 142.5 – 157.5 mg / tablet
Microbial Contamination** **Total aerobic microbial count** **Total yeast and mould count** ***Escherichia coli***	 **Complies with Ph.Eur.** **Not greater than 10^3 cfu/g** **Not greater than 10^2 cfu/g** **Absent in 1 g**

* For the control of water and ethanol

** The test is not routinely performed. A minimum of two batches will be tested annually during release testing. During stability studies the tests will be performed at the beginning and annually thereafter

DA

3.2.P.5.1 Specifications_Shelf Life

Test	Limit
Description	White to pale yellow, round, flat, bevel edged tablets
Test for identity by HPLC	The principal peak in the HPLC chromatogram of the sample corresponds with the peak produced by a reference standard of ranitidine hydrochloride
Disintegration time	Complies with the requirements of the European Pharmacopoeia
~~Uniformity of weight~~	~~Complies with the requirements of the European Pharmacopoeia~~
~~Related impurities by TLC (% w/w of nominal ranitidine content)~~ ~~Principal impurity~~ ~~Second impurity~~ ~~Total impurities~~	 ~~≯ 0.7~~ ~~≯ 0.5~~ ~~≯ 1.5~~
Ranitidine content by HPLC (% of label claim)	95 – 105

A

3.2.P.5.1 Specifications_Shelf Life

Test	Limit
Description[1]	White to pale yellow, round, bevelled tablet **marked "GS LHK" on one side and flat on the other**
Identity of Ranitidine Hydrochloride by HPLC **by UV**	 The principal peak in the HPLC chromatogram of the sample corresponds with the peak produced by a reference standard of ranitidine hydrochloride. **The UV spectrum obtained with the sample solution compares to that of the reference substance.**
Disintegration time	Complies with Ph.Eur. **NMT 5 minutes**
Uniformity of Dosage Units	**Complies with Ph.Eur.**
Loss on Drying	**NMT 0.5%***
Related impurities by HPLC (% w/w of nominal Ranitidine content) **RRT 0.66** **Any other impurity** **Total impurities**	 **NMT0.5** **NMT 0.2** **NMT 1.0**
Assay Ranitidine content by HPLC	95 – 105% L.S. 142.5 – 157.5 mg / tablet
Microbial Contamination** **Total aerobic microbial count** **Total yeast and mould count** ***Escherichia coli***	 **Complies with Ph.Eur.** **Not greater than 10^3 cfu/g** **Not greater than 10^2 cfu/g** **Absent in 1 g**

* For the control of water and ethanol

** The test is not routinely performed. A minimum of two batches will be tested annually during release testing. During stability studies the tests will be performed at the beginning and annually thereafter

Compresse 300 mg

DA

3.2.P.5.1 Specifications_Release

Test	Limit
Description	White to pale yellow, round, flat, bevel edged tablets
Test for identity by HPLC	The principal peak in the HPLC chromatogram of the sample corresponds with the peak produced by a reference standard of ranitidine hydrochloride
pH of solution	6.0 - 6.5
Disintegration time	Complies with the requirements of the European Pharmacopoeia
~~Uniformity of weight~~	~~Complies with the requirements of the European Pharmacopoeia~~
~~Water content (% w/w)~~	~~0.5~~
~~Residual solvents by GC (% w/w)~~	~~0.2~~
~~Related impurities by TLC (% w/w of nominal ranitidine content)~~ ~~Principal impurity~~ ~~Second impurity~~ ~~Total impurities~~	 ~~0.5~~ ~~0.3~~ ~~1.0~~
Ranitidine content by HPLC (% of label claim)	95 – 105

A

3.2.P.5.1 Specifications_Release

Test	Limit
Description[1]	White to pale yellow, round, bevelled tablet **marked "GS MJG" on one side and flat on the other**
Identity of Ranitidine Hydrochloride by HPLC **by UV**	 The principal peak in the HPLC chromatogram of the sample corresponds with the peak produced by a reference standard of ranitidine hydrochloride. **The UV spectrum obtained with the sample solution compares to that of the reference substance.**
pH of solution	6.0 - 6.5
Disintegration time	Complies with Ph.Eur. **NMT 5 minutes**
Uniformity of Dosage Units	**Complies with Ph.Eur.**
Loss on Drying	**NMT 0.5%***
Related impurities by HPLC (% w/w of nominal Ranitidine content) **RRT 0.66** **Any other impurity** **Total impurities**	 **NMT0.2** **NMT 0.2** **NMT 0.5**
Assay Ranitidine content by HPLC	95 – 105% L.S. 285.0 – 315.0 mg / tablet
Microbial Contamination** **Total aerobic microbial count** **Total yeast and mould count** ***Escherichia coli***	 **Complies with Ph.Eur.** **Not greater than 10^3 cfu/g** **Not greater than 10^2 cfu/g** **Absent in 1 g**

* For the control of water and ethanol

** The test is not routinely performed. A minimum of two batches will be tested annually during release testing. During stability studies the tests will be performed at the beginning and annually thereafter

DA

3.2.P.5.1 Specifications_Shelf Life

Test	**Limit**
Description	White to pale yellow, round, flat, bevel edged tablets
Test for identity by HPLC	The principal peak in the HPLC chromatogram of the sample corresponds with the peak produced by a reference standard of ranitidine hydrochloride
Disintegration time	Complies with the requirements of the European Pharmacopoeia
~~Uniformity of weight~~	~~Complies with the requirements of the European Pharmacopoeia~~
~~Related impurities by TLC (% w/w of nominal ranitidine content)~~ ~~Principal impurity~~ ~~Second impurity~~ ~~Total impurities~~	 ~~0.7~~ ~~0.5~~ ~~1.5~~
Ranitidine content by HPLC (% of label claim)	95 – 105

A

3.2.P.5.1 Specifications_Shelf Life

Test	**Limit**
Description[1]	White to pale yellow, round, bevelled tablet **marked "GS MJG" on one side and flat on the other**
Identity of Ranitidine Hydrochloride by HPLC **by UV**	 The principal peak in the HPLC chromatogram of the sample corresponds with the peak produced by a reference standard of ranitidine hydrochloride. **The UV spectrum obtained with the sample solution compares to that of the reference substance.**
Disintegration time	Complies with Ph.Eur. **NMT 5 minutes**
Uniformity of Dosage Units	**Complies with Ph.Eur.**
Loss on Drying	**NMT 0.5%***
Related impurities by HPLC **(% w/w of nominal Ranitidine content)** **RRT 0.66** **Any other impurity** **Total impurities**	 **NMT0.5** **NMT 0.2** **NMT 1.0**
Assay Ranitidine content by HPLC	95 – 105% L.S. 285.0 – 315.0 mg / tablet
Microbial Contamination** **Total aerobic microbial count** **Total yeast and mould count** ***Escherichia coli***	**Complies with Ph.Eur.** **Not greater than 10^3 cfu/g** **Not greater than 10^2 cfu/g** **Absent in 1 g**

* For the control of water and ethanol

** The test is not routinely performed. A minimum of two batches will be tested annually during release testing. During stability studies the tests will be performed at the beginning and annually thereafter

relativamente alla specialità medicinale indicata in oggetto e alle confezioni sotto elencate:

024448072 - «150 mg compresse effervescenti» 20 compresse; 024448096 - «300 mg compresse effervescenti» 10 compresse.

I lotti già prodotti possono essere mantenuti in commercio fino alla data di scadenza indicata in etichetta.

La presente determinazione ha effetto dal giorno successivo a quello della sua pubblicazione nella *Gazzetta Ufficiale* della Repubblica italiana.

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