Acute non-Q-wave myocardial infarction: a distinct clinical entity of increasing importance

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Despite the increasing incidence of acute non-Q-wave myocardial infarction, controversy remains regarding its validity as a distinct pathophysiologic and clinical entity. Review of the data indicates that the controversy is more apparent than real. The pathophysiologic factor discriminating best between non-Q-wave and Q-wave infarction is the incidence rate of total occlusion of the infarct-related artery, approximately 30% in non-Q-wave infarction and 80% in Q-wave infarction. Patients with non-Q-wave infarction have a higher incidence of pre-existing angina than patients with Q-wave infarction; they also have lower peak creatine kinase levels, higher ejection fractions and lower wall-motion abnormality scores, which suggests a smaller area of acute infarction damage. However, patients with non-Q-wave infarction have a significantly shorter time to peak creatine kinase level and more heterogeneous ventriculographic and electrocardiographic infarct patterns. The in-hospital death rate is lower in non-Q-wave than in Q-wave infarction (approximately 12% v. 19%). The long-term death rates are similar for the two groups (27% and 23%), but the incidence of subsequent coronary events is higher among patients with non-Q-wave infarction; in particular, reinfarction is an important predictor of risk of death. Most of the differences in biologic and clinical variables between the two types of acute infarction can be related to a lower incidence of total occlusion, earlier reperfusion or better collateral supply in non-Q-wave infarction. Further study is needed to better characterize the long-term risk and to define the most appropriate therapies.

Malgré l'augmentation de la fréquence de survenue d'infarctus aigu du myocarde sans onde Q pathologique, on discute encore la question de savoir s'il constitue une entité physiopathologique et clinique à part. La controverse est plus apparente que réelle si on considère les faits. Le facteur qui distingue le plus nettement ce genre d'infarctus de celui qui s'accompagne d'une onde Q pathologique est la fréquence de l'occlusion complète de l'artére en cause: environ 30% dans l'un et 80% dans l'autre. Les porteurs d'infarctus sans altération de l'onde Q, par rapport aux autres, auront plus souvent présenté de l'angor au préalable; ils montrent des pics moins élevés de la créatine-kinase, de meilleures fractions d'éjection et des indices plus bas de dyskinésie ventriculaire, le tout faisant penser à des lésions aiguës plus circonscrites. Chez ces sujets, cependant, le pic de la créatine-kinase est atteint plus vite, et leurs tableaux ventriculographiques et électrocardiographiques sont plus hétérogènes. Si leur taux de mortalité hospitalière est plus basse (environ 12% contre 19%), le taux de mortalité à longue échéance est comparable dans les deux groupes (27% et 23%). Mais les porteurs d'infarctus sans onde Q pathologique présenteront, par la suite, plus d'épisodes coronariens, notamment d'infarctus itératif qui constitue un net risque mortel. La plupart des différences

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cliniques et biologiques entre les deux genres d'infarctus reposent sur la moindre fréquence d'occlusion totale, la reperfusion précoce ou la meilleure circulation collatérale qu'on observe dans l'infarctus sans onde Q pathologique. La poursuite de ce genre d'étude permettra de mieux cerner les risques à longue échéance et d'adapter le traitement.

In practice, the diagnosis of acute myocardial infarction is based on a history of cardiac-type pain, diagnostic elevation of serum enzyme levels and electrocardiographic (ECG) abnormalities. In the clinical setting acute myocardial infarction is classified by means of 12-lead ECG criteria.[1] Currently the most widely used ECG infarct designations are non-Q-wave[2] and Q-wave,[3] the latter group usually being divided into anterior and inferior subgroups. Anterior Q-wave infarction is defined principally by the presence of abnormal Q waves (lasting 0.04 seconds or more) in any combination of leads I, aV_L and V_1 to V_6 and inferior Q-wave infarction by abnormal Q waves in leads II and aV_F.[3] Non-Q-wave infarction is defined as evidence of infarction in the absence of abnormal Q waves in any of these leads.[2] In none of the three ECG designations are repolarization (ST-segment, T-wave) abnormalities usually part of the classification criteria. The current terminology, although limited, is at least simple and reproducible. The key question is, Is it meaningful?

Although there has been some controversy about the present classification scheme, particularly regarding the validity of non-Q-wave myocardial infarction as a distinct clinical entity,[4] critical review of the recent literature suggests that the controversy is more apparent than real. Moreover, the available evidence suggests that the differences between Q-wave and non-Q-wave infarction, particularly in prognosis and changing incidence, have important clinical implications that make their understanding imperative to the practising physician.

In this paper we compare Q-wave and non-Q-wave infarction from several perspectives, focusing on the relevant differences. We reviewed all original references and tried to standardize, as much as possible, the various definitions of Q-wave and non-Q-wave infarction. In particular, we considered all patients with non-Q-wave infarction as a common group, irrespective of the reported patterns of ST-segment and T-wave abnormalities. If the original studies did not specifically evaluate the relative incidence of the selected variables and if the raw data were given, we performed chi-square testing to estimate statistical significance.

Pathophysiologic features

Part of the present controversy derives from the clinical use of ill-defined pathological nomenclature. Non-Q-wave infarction was often previously termed nontransmural or subendocardial, and Q-wave infarction was termed transmural. The issue has been further clouded by various morphologic definitions of nontransmural injury.[5] "Subendocardial" has, for example, been defined as ranging from the inner one-quarter to the inner three-quarters of the ventricular wall thickness.[5] In a postmortem morphologic study Freifeld and colleagues[5] rigidly defined "transmural" as full-thickness injury and compared the necrosis patterns in patients with transmural and with less than full-thickness (nontransmural) injury. They found a greater incidence of contraction-band necrosis in the nontransmural specimens and concluded that this was compatible with a higher incidence of reperfusion injury in patients with true nontransmural infarction than in those with transmural infarction. Thus, there may be a more basic common denominator to the spatial and morphologic patterns of ventricular wall injury than degree of wall thickness involved in acute infarction.

The most relevant point is that acute non-Q-wave infarction, however named, has always been clinically defined by the absence of infarct-associated Q waves on the 12-lead ECG. Q waves do not necessarily mean full-thickness injury in acute infarction, and the absence of Q waves does not necessarily mean less than full-thickness injury.[1] To infer the degree of mural damage or to localize the injury to the subendocardial layers is more than can reliably or reasonably be deduced from the 12-lead ECG.[1,5]

The evidence emerging from several studies indicates that the pathophysiologic factor discriminating best between Q-wave and non-Q-wave myocardial infarction is the incidence of acute total occlusion of the infarct-related artery (Table I).[6-13] Over a relatively wide range of timing of angiographic studies approximately 70% to 80% of patients with Q-wave infarction had complete occlusion of the infarct-related artery, compared with about 20% to 40% of patients with non-Q-wave infarction. DeWood and associates[12] also found a high degree of collateral supply to infarct-related arteries in acute non-Q-wave myocardial infarction; this finding may partly explain the morphologic reperfusion injury pattern (contraction-band necrosis) found in true nontransmural infarction.[5] Interestingly, among patients with non-Q-wave infarction DeWood and associates found a significantly higher rate of total occlusion later in the postinfarction course (42% at 3 to 7 days v. 26% at less than 24 hours). In contrast, in a previous study a lower incidence of total occlusion with time after Q-wave infarction was found. Pichard and coworkers[9] also reported a decreased incidence rate of total coronary occlusion with time after Q-wave infarction (80% at 2 to 4 weeks v. approximately 40% at 12 months). These findings suggest that although the rates of patency of the affected artery in the two types of infarction are markedly different in the earliest phase, the inci-

dence may become similar with time. The clinical outcome data are compatible with this hypothesis.

Clinical presentation

Patients with non-Q-wave myocardial infarction appear to have a significantly higher incidence of pre-existing angina than patients with Q-wave infarction. Review of the data from four studies revealed that, on average, angina occurred in 38% of patients who subsequently had Q-wave infarction, compared with 52% of patients with non-Q-wave infarction.[10,13-15] A higher incidence of pre-existing angina in patients with non-Q-wave infarction is also compatible with more severe coronary artery stenosis and a coexistent increased potential for collateral coronary artery development.[12]

In almost all the published studies patients with non-Q-wave myocardial infarction had lower peak levels of creatine kinase and other enzymes than patients with Q-wave infarction.[2,3,7,10,13-16] Furthermore, in first acute infarctions patients with non-Q-wave infarction had left ventricular ejection fractions and scores for depolarization, repolarization and wall-motion abnormality that were quantitatively similar to those of patients with inferior Q-wave infarction.[2] In contrast, patients with anterior Q-wave infarction had significantly greater ECG and ventriculographic abnormality scores than patients with inferior Q-wave infarction or non-Q-wave infarction.[2]

In general, the available evidence strongly supports a smaller acute-phase ischemic injury in non-Q-wave infarction than in Q-wave infarction.[2,3,7,10,13-16] This finding is what one might expect with a lower incidence of acute total occlusion, earlier reperfusion or better collateral filling of the infarct-related artery. As well, the time to peak creatine kinase level from onset of symptoms is shorter in patients with non-Q-wave myocardial infarction;[10,13,17] this, too, is not unexpected if earlier reperfusion[5] or greater collateral supply[12] occurs in such patients.

Body surface ECG map and radionuclide ventriculographic studies have also revealed different ECG and ventriculographic spatial patterns among the infarction groups.[2,3] In particular, there is greater heterogeneity of wall motion among patients with non-Q-wave infarction, including normal wall motion, as well as several Q-wave patterns, ranging from "missed" anterior, inferior and posterior Q-wave infarction to normal or near-normal patterns of "true" non-Q-wave infarction.[2] These spatial and quantitative differences support the concept that non-Q-wave infarction is a distinct clinical entity and suggest that the size and location of the acute-phase injury are major determinants of the genesis and detection of infarct-associated Q waves.[2,3]

Furthermore, the evidence suggests that the degree and timing of coronary artery disease are different in acute Q-wave infarction and acute non-Q-wave infarction. In the former, sudden occlusive formation of thrombi on coronary atherosclerotic plaque is the main cause of infarction. In the latter, the event leading to infarction is not so obvious. The evidence is, however, compatible with a complex, dynamic interaction of plaque and gradually and transiently or only partially occlusive clot in the infarct-related artery, with efficient collateral supply to its distal segments.

Prognosis

In any consideration of myocardial infarction the most important clinical variable is mortality. The average acute-phase or in-hospital death rate in 13 published studies was 19% for Q-wave infarction and 12% for non-Q-wave infarction (Table II).[14-16,18-27] In 6 of the 13 studies the in-hospital death rate was significantly lower for non-Q-wave infarction than for Q-wave infarction.[16,20-22,24,27] Only one study revealed a higher early death rate for non-Q-wave infarction than for Q-wave infarction.[18]

The average postdischarge, or long-term, death rate in nine studies published since 1975

Table I — Reported incidence rates of total occlusion of the presumed infarct-related artery in acute Q-wave and non-Q-wave myocardial infarction

Investigator	Timing of angiography after infarction	Incidence rate, %		p*
		Q-wave infarction	Non-Q-wave infarction	
Fuster et al[6]	< 1 yr	79	48	< 0.001†
Schulze et al[7]	10–24 d	18	18	NS
Marmor et al[8]	< 48 d	83	26	< 0.001†
Pichard et al[9]	2–4 wk	80	8	< 0.001†
Gibson et al[10]	11 ± 3 d	75	46	< 0.0001
DeWood et al[11]	< 4 h	87	–	–
DeWood et al[12]	< 24 h	–	26	–
Huey et al[13]	10 ± 3 d	76	43	0.001

*NS = not significant.
†Not specifically tested in original reference.

was 23% for Q-wave infarction and 28% for non-Q-wave infarction (Table III).[10,14,15,20,23,25,27-29] In two studies the rate was significantly higher for non-Q-wave infarction than for Q-wave infarction.[15,23] Overall, the available evidence indicates relatively comparable long-term death rates for the two groups. The data suggest, however, that if larger groups were studied for longer periods a greater long-term risk might become apparent with non-Q-wave infarction.

The incidence of other important clinical variables, including postinfarction angina, reinfarction and need for coronary artery bypass surgery, appears to be higher in patients with non-Q-wave infarction than in those with Q-wave infarction.[10,15,24-26,30] The average incidence of reinfarction in five studies was 6% for Q-wave infarction and 21% for non-Q-wave infarction (Table IV).[10,24-26,30] Moreover, early reinfarction or extension of non-Q-wave infarction appears to be an important

Table II — Reported in-hospital death rates in acute Q-wave and non-Q-wave myocardial infarction

Investigator	Death rate, %		p*
	Q-wave infarction	Non-Q-wave infarction	
Rigo et al[14]	22	13	NS
Cannom et al[15]	17	8	NS
Strauss et al[16]	17	4	< 0.02
Scheinman et al[18]	19	38	< 0.02†
Madias et al[19]	10	9	NS
Szklo et al[20]	30	18	< 0.01
Schröter et al[21]	28	11	< 0.05
Thanavaro et al[22]	11	3	< 0.01
Mahony et al[23]	17	11	NS
Hutter et al[24]	20	9	< 0.04
Maisel et al[25]	10	8	NS
Ogawa et al[26]	17	17	NS
Goldberg et al[27]	25	12	< 0.05

*NS = not significant.
†Not specifically tested in original reference.

Table III — Reported long-term death rates in acute Q-wave and non-Q-wave myocardial infarction

Investigator	Death rate, %		p*
	Q-wave infarction	Non-Q-wave infarction	
Gibson et al[10]	8	9	NS
Rigo et al[14]	18	19	NS
Cannom et al[15]	30	47	< 0.05
Szklo et al[20]	27	28	NS
Mahony et al[23]	28	40	< 0.01†
Maisel et al[25]	19	21	NS†
Goldberg et al[27]	12	15	NS
Fabricius-Bjerre et al[28]	41	52	NS†
Krone et al[29]	20	17	NS

*NS = not significant.
†Not specifically tested in original reference.

Table IV — Reported reinfarction rates in acute Q-wave and non-Q-wave myocardial infarction

Investigator	Length of follow-up	Reinfarction rate, %		p*
		Q-wave infarction	Non-Q-wave infarction	
Gibson et al[10]	30 mo	7	18	< 0.01
Hutter et al[24]	9 mo	2	21	< 0.001†
Maisel et al[25]	In hospital	6	8	NS
Ogawa et al[26]	25 mo	8	17	< 0.05
Marmor et al[30]	14 d	8	43	< 0.001†

*NS = not significant.
†Not specifically tested in original reference.

clinical predictor of risk of death. Marmor and collaborators[30] found an in-hospital death rate of 16% among patients with early extension of non-Q-wave infarction, compared with 7% among patients with no extension. Maisel and colleagues[25] reported a 1-year death rate of 24% among patients who had extension of non-Q-wave infarction, significantly different from the rate among patients without early extension, 6%; in contrast, early extension was not found to be predictive of increased risk of death in patients who presented with Q-wave infarction.

The reported group-specific differences in rates of death and disease further support the concept of an essential pathophysiologic difference between Q-wave and non-Q-wave infarction. The evidence suggests that in non-Q-wave infarction the affected artery, although not totally occluded, or only transiently occluded, markedly and acutely compromises coronary blood flow and that this artery may again compromise flow, with consequent clinical events, in the postinfarction period.

Epidemiologic features

Perhaps of equal importance to recent knowledge defining the pathophysiologic and clinical features of non-Q-wave infarction is the epidemiologic evidence that the incidence of the syndrome may be increasing, both naturally and iatrogenically. In almost all the published studies in which recruitment was done at the same time the ratio of the incidence rates of Q-wave and non-Q-wave infarction was about 3:1 to 5:1.[6-10,13-16,18-20,22,23,25-27,31] In the most recent study of changes in the occurrence of the two types of infarction Goldberg and associates[27] found that the age-adjusted hospital attack rate (per 100 000) for Q-wave infarction increased significantly between 1975 and 1981, from 153 to 197; the attack rate for non-Q-wave infarction increased even more, from 46 to 89. The authors concluded that the findings indicated a significant change in either the occurrence or the recognition rates of non-Q-wave myocardial infarction.

The apparently increased incidence of non-Q-wave infarction may be related to the recent widespread adoption of antiplatelet, anticoagulant and other aggressive therapies for the management of the acute intermediate ischemic syndromes (unstable angina, coronary insufficiency and possible myocardial infarction). Certainly patients with these syndromes appear to have coronary anatomy[32,33] and risks of death and sickness[34,35] similar to those of patients with non-Q-wave infarction. It seems reasonable to speculate that successful therapy, although possibly avoiding acute Q-wave infarction and death, may predispose patients to subsequent non-Q-wave infarction.

Similarly, if one accepts the concept that the underlying coronary artery defect in acute non-Q-wave myocardial infarction is the critically compromised lumen of the infarct-related artery,[6-13] it seems appropriate to speculate that patients who have received successful thrombolytic therapy for acute myocardial infarction have similar pathophysiologic features. Angiography in such patients soon after thrombolytic therapy revealed a high incidence of patent but severely narrowed infarct-related arteries.[36,37] Moreover, there appears to be a significant risk of subsequent extension or reinfarction in these patients (11% to 14%).[36] A recent meta-analysis of the pooled data of 27 intravenous and 9 intracoronary fibrinolytic therapy studies revealed that the relative risk of reinfarction in the treated groups was 57% higher in the intravenous studies and 100% higher in the intracoronary studies (Salim Yusuf: personal communication, 1986). These data take into account the increased relative risk of reinfarction after non-Q-wave infarction.[10,24-26,30] The rapidly increasing use of such agents may be producing a large pool of patients whose postlytic infarct-related coronary anatomy and risk of reinfarction are similar to those of patients with acute non-Q-wave myocardial infarction.

Effective therapy for these clinical syndromes would obviously benefit an already large, and probably increasing, patient population.

Therapy

Although no studies have specifically examined reduction of postinfarct mortality in patients with non-Q-wave myocardial infarction, numerous studies have evaluated several interventions for patients with acute infarction as a whole. Several individual studies of β-blockers[38] and meta-analysis of pooled data on β-blockers, antiplatelet medications and nitrates (Salim Yusuf: personal communication, 1986) have indicated significant reductions in the risk of death after infarction, in the range of 10% to 33%. Retrospective subgroup analysis in studies of timolol also showed a reduction in postinfarction death rates for the non-Q-wave population.[39,40] On the other hand, the Beta-Blocker Heart Attack Trial revealed no reduction in risk of death after infarction for the non-Q-wave subgroup.[41]

Individual studies[39] and meta-analysis (Salim Yusuf: personal communication, 1986) suggest that β-blockers and acetylsalicylic acid (ASA) reduce the risk of reinfarction by approximately 20% to 30%. In addition, Klimt and coworkers[42] reported a reduction in the incidence of subsequent coronary events (nonfatal myocardial infarction plus death due to a coronary event) of 30% in patients taking ASA plus dipyridamole after an initial myocardial infarction. Study of subgroups defined a priori suggested that the beneficial effects of the therapy were greater in patients with non-Q-wave infarction than in those with Q-wave infarction.

Gibson and collaborators[43] specifically addressed the question of reduction of reinfarction

risk with diltiazem hydrochloride after non-Q-wave infarction and found a significant reduction in the reinfarction rate up to day 14. However, there was no significant difference in the death rate between the patients who received diltiazem and those who did not. Meta-analysis of therapy with various calcium antagonists after infarction has, in fact, revealed a disturbing excess mortality, averaging 6%, among patients taking the active agents.[44] Therefore, although specific calcium antagonists may protect against reinfarction early after acute non-Q-wave infarction, their long-term use in this setting cannot as yet be advocated.

At present, the evidence suggests that patients who survive non-Q-wave infarction can safely be given β-blockers, ASA and nitrates on a long-term basis with a reasonable expectation of enhanced survival and a decreased risk of reinfarction. Diltiazem may also be beneficial in the short term. Optimal further management is not completely certain but should obviously include careful clinical follow-up and assessment of risk, based on evidence of reinfarction and tests of left ventricular function, exercise tolerance and cardiac rhythm. However, these tests have not been shown to be effective discriminators of the specific risk for patients with non-Q-wave infarction. Because of this and the overall high levels of risk, it may also be appropriate to consider early invasive investigation and possible operative interventions in such patients.[45] Further study of risk stratification and clinical trials of operative and nonoperative therapies in patients with non-Q-wave infarction are needed.

We thank Gaye E. Strong and Colleen M. Sloan for expert secretarial assistance.

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Indications and Clinical use – Zantac Tablets are indicated for the treatment of all conditions where a controlled reduction of gastric secretion is required for the rapid relief of pain and/or ulcer healing. These include duodenal ulcer, benign gastric ulcer and reflux oesophagitis.

Contraindications – Zantac is contraindicated for patients known to have hypersensitivity to the drug.

Warnings – ***Gastric ulcer*** – Treatment with a histamine H_2-antagonist may mask symptoms associated with carcinoma of the stomach and therefore may delay diagnosis of the condition. Accordingly, where gastric ulcer is suspected the possibility of malignancy should be excluded before therapy with Zantac Tablets is instituted.

Precautions – ***Use in pregnancy and nursing mothers*** – The safety of Zantac in the treatment of conditions where a controlled reduction of gastric secretion is required during pregnancy has not been established. Reproduction studies performed in rats and rabbits have revealed no evidence of impaired fertility or harm to the foetus due to Zantac. If the administration of Zantac is considered to be necessary, its use requires that the potential benefits be weighed against possible hazards to the patient and to the foetus. Ranitidine is secreted in breast milk in lactating mothers but the clinical significance of this has not been fully evaluated.

Use in impaired renal function – Ranitidine is excreted via the kidney and in the presence of severe renal impairment, plasma levels of ranitidine are increased and prolonged. Accordingly, in the presence of severe renal impairment, clinicians may wish to reduce the dose to a half of the usual dose taken twice daily.

Children – Experience with Zantac Tablets in children is limited and such use has not been fully evaluated in clinical studies. It has however been used successfully in children aged 8-18 years in doses up to 150 mg twice daily without adverse effect.

Interactions with other drugs – Although ranitidine has been reported to bind weakly to cytochrome P450 in vitro, recommended doses of the drug do not inhibit the action of the cytochrome P450-linked oxygenase in the liver. There are conflicting reports in the literature about possible interactions between ranitidine and several drugs; the clinical significance of these reports has not been substantiated. Amongst the drugs studied were warfarin, diazepam, metoprolol and nifedipine.

Adverse Reactions – Headache, rash, dizziness, constipation, diarrhoea and nausea have been reported in a very small proportion of drug-treated patients but these also occurred in patients receiving placebo. A few patients on re-challenge with Zantac have had a recurrence of skin rash, headache or dizziness. Some increases in serum transaminases and gamma-glutamyl transpeptidase have been reported which have returned to normal either on continued treatment or on stopping Zantac. In placebo controlled studies involving nearly 2,500 patients, there was no difference between the incidence of elevations of SGOT and/or SGPT values in the Zantac-treated or placebo-treated groups. Rare cases of hepatitis have been reported but have been transient and no causal relationship has been established.

Anaphylactoid reactions (anaphylaxis, urticaria, angioneurotic oedema, bronchospasm) have been seen rarely following the parenteral and oral administration of Zantac. These reactions have occasionally occurred after a single dose.

Decreases in white blood cell count and platelet count have occurred in a few patients. Other haematological and renal laboratory tests have not revealed any drug related abnormalities.

No clinically significant interference with endocrine or gonadal function has been reported.

Symptoms and Treatment of Overdosage – No particular problems are expected following overdosage with Zantac. Symptomatic and supportive therapy should be given as appropriate. If need be, the drug may be removed from the plasma by haemodialysis.

Dosage and Administration – ***Adults:*** Duodenal ulcer and benign gastric ulcer: 300 mg once daily, at bedtime. It is not necessary to time the dose in relation to meals. In most cases of duodenal ulcer and benign gastric ulcer, healing will occur in four weeks. In the small number of patients whose ulcers may not have fully healed, these are likely to respond to a further course of treatment.

Patients who have responded to this short term therapy, particularly those with a history of recurrent ulcer, may usefully have extended maintenance treatment at a reduced dosage of one 150 mg tablet at bedtime.

To help in the management of reflux oesophagitis, the recommended course of treatment is one 150 mg tablet twice daily for up to 8 weeks.

Experience with Zantac in children is limited and it has not been fully evaluated in clinical studies – see **Precautions.**

Availability – Zantac Tablets are available as white film-coated tablets engraved ZANTAC 150 on one face and GLAXO on the other, containing 150 mg ranitidine (as the hydrochloride), in packs of 28 and 56 tablets.

Zantac Tablets are also available as white, capsule shaped, film-coated tablets engraved ZANTAC 300 on one face and GLAXO on the other, containing 300 mg ranitidine (as the hydrochloride) packed in cartons containing 28 tablets.

Zantac Injection is available as 2 mL ampoules each containing 50 mg ranitidine (as the hydrochloride) in 2 mL solution for intravenous or intramuscular administration. Packages of 10 ampoules.

References

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